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(21) International Application Number: PCT/US97/14559 (22) International Filing Date: 20 August 1997 (20.08.97) (30) Priority Data: 60/024,559 26 August 1996 (26.08.96) US (71) Applicant (for all designated States except US): ELI LILLY AND COMPANY [US/US]; Lilly Corporate Center, Indi- anapolis, IN 46285 (US). (72) Inventor; and (75) Inventor/Applicant (for US only): HOLLINSHEAD, Sean, P. [GB/US], 1201 North Street, Durham, NC 27701 (US). (74) Agents: COLLINS, Daniel, W. et al.; Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report.
(54) Title: COMBINATORIAL PROCESS FOR PREPARING SUBSTITUTED PYRROLIDINE LIBRARIES (57) Abstract This invention relates to a novel solid phase process for the preparation of pyrrolidine combinatorial libraries. These libraries have use for drug discovery and are used to form wellplate components of novel assay kits.		

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COMBINATORIAL PROCESS FOR PREPARING SUBSTITUTED PYRROLIDINE LIBRARIES

This application claims the benefit of U.S. Provisional
5 Patent Application Serial No. 60/024,559, filed August 26,
1996.

Field of the Invention

This invention relates to the preparation of libraries
10 of substituted pyrrolidines by combinatorial processes.
These libraries are useful for discovery of lead compounds
for drug development and improved assay kits.

Background of the Invention

15 Traditional chemical synthesis for drug discovery is
done by individually creating, isolating, and identifying
candidate compounds. Companies have long relied on their
historical collections of compounds and compound collections
from exchange agreements as sources of diverse structures
20 for generating lead pharmaceutical compounds.

All of these historical approaches have drawbacks.
Corporate collections of compounds may have a certain bias
and medicinal chemists using traditional synthetic
techniques cannot synthesize hundreds or thousands of
25 diverse compounds to find promising leads.

Combinatorial chemistry is a relatively new technique
for chemical synthesis. It fills the longfelt need for a
method to quickly generate highly diverse non-peptide
compound libraries. Generally, diverse libraries contain
30 compounds with a common core or scaffold which are
substituted with a great variety of substituents. More
recently, modern drug discovery has used the methods of
combinatorial chemistry to generate large numbers (viz.,

about 10^2 to 10^6) of compounds generically referred to as "libraries."

Combinatorial chemistry may be performed in a manner where libraries of compounds are generated as mixtures with complete identification of individual compounds postponed until after positive screening results are obtained. However, a preferred form of combinatorial chemistry is "parallel array synthesis" where individual reaction products (most often individual compounds) are synthesized together, but are retained in separate vessels. For example, the library compounds are held in the individual wells of 96 well microtiter plates. Use of standardized microtiter plates or equivalent apparatus is advantageous because such apparatus is readily manipulated by programmed robotic machinery.

Generally, combinatorial chemistry is conducted on a solid phase support, normally a polymer. A selected scaffold is cleavably tethered to the solid support by a chemical linker. Reactions are carried out to modify the scaffold while tethered to the solid support. In a final step, the product is cleaved and released from the solid support.

Combinatorial chemistry evidences its utility by commercial success. Millions of dollars have been spent for recent purchases or cooperative associations of major pharmaceutical companies with small companies specializing in combinatorial chemistry (e.g., Glaxo's acquisition of Affymax, Marion Merrell Dow's purchase of Selectide, Proctor & Gamble with Houghten, Astra with Alanex, Pfizer with Oxford Asymmetry, Sandoz with Pharmacopeia, Solvay with Argule, CIBA with Chiron, and Eli Lilly with Sphinx Pharmaceutical).

Certain chemical reactions of pyrrolidines are known.

Various aspects of pyrrolidine chemistry are known in the prior art as set out below:

A) The article, "Synthesis of Enantiomerically Pure Pyrrolidines by Stereospecific Cycloaddition of Azomethine Ylides with Enones," by Patzel, M. et al., Tetrahedron Letters., Vol. 34, No. 36, pp. 5707-5710, 1993 describes the synthesis of pyrrolidines via cycloaddition onto enones.

B) The article, "Improved Synthesis of 4-Alkoxybenzyl Alcohol Resin" by Gui-shen Lu, et. al., J. Org. Chem., 1981, vol. 46, pp. 3433-3436, describes the preparation of a Wang resin for solid-phase peptide synthesis.

C) The article, "Combinatorial Organic Synthesis of Highly Functionalized Pyrrolidines: Identification of a Patent Angiotensin Converting Enzyme Inhibitor from a Mercaptoacyl Proline Library", by Martin M. Murphy, et. al., J. Am. Chem. Soc. 1995, Vol 117, pp. 7029-7030 describes the preparation of selected functionalized pyrrolidines using 1,3-dipolar cycloaddition reactions.

D) The article, "Solid-Phase Synthesis of Proline Analogs via a Three Component 1,3-dipolar cycloaddition" by Bruce C. Hamper, et. al. Tetrahedron Letters, Vol. 37, No. 21, pages 3671-3674, 1996, describes the preparation of selected highly substituted pyrrolidines by solid phase synthesis using 1,3-dipolar cycloaddition of a resin bound azomethine ylide.

To continue exploration of new libraries for
pharmaceutical and agricultural lead compounds it is
necessary to develop new chemistries which permit chemical novel scaffolds to be functionalized with highly diverse groups.

Summary of the Invention

Combinatorial chemistry may be used at two distinct phases of drug development. In the discovery phase highly diverse libraries are created to find lead compounds. In
5 a second optimization phase, strong lead compounds are much more narrowly modified to find optimal molecular configurations. The method of this invention has applicability for making both diverse libraries of pyrrolidine compounds useful for finding new lead
10 compounds and directed libraries of pyrrolidine compounds useful for optimizing a particular desired biological activity.

This invention is an improved combinatorial process for making a library of pyrrolidine compounds.

15 This invention is also the combinatorial library of pyrrolidine compounds.

This invention is also a library of intermediate substituted solid supported pyrrolidine library compounds.

This invention is also the individual pyrrolidine
20 compounds in the pyrrolidine combinatorial library of the invention.

This invention is also a novel wellplate apparatus containing the novel pyrrolidine library compounds of the invention.

25 This invention is also an assay kit for identification of pharmaceutical lead pyrrolidine compounds, said kit comprising (i) wellplate apparatus, and (ii) biological assay reagents, said wellplate apparatus having a combinatorial library compound in each well; wherein the
30 improvement comprises using as a wellplate a combinatorial pyrrolidine wellplate apparatus where each well contains a pyrrolidine compound prepared by the process of the invention.

Brief Description of the Drawings

FIG. 1 is a top view of a wellplate apparatus.

FIG. 2 is a side view of a wellplate apparatus.

5

Detailed Description of the Invention

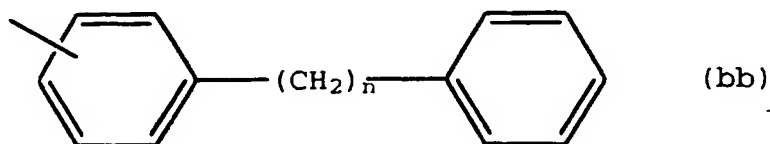
I. Definitions:

The following terms have the meaning defined below when
10 used in this specification of the invention:

"Acidic group" means a proton donor substituent typified by $-CO_2H$, $-SO_3H$, and $-P(O)(OH)_2$.

"Aromatic group" means a substituted or unsubstituted heterocyclic group derived from pyrrolyl, furanyl,
15 thiophenyl, pyrazolyl, imidazolyl, phenylimidazolyl, triazolyl, isoxazolyl, oxazolyl, thiazolyl, thiadiazolyl, indolyl, carbazolyl, norharmanyl, azaindolyl, benzofuranyl, dibenzofuranyl, dibenzothiophenyl, indazolyl, imidazo(1,2-pyridinyl, benzotriazolyl, anthranilyl, 1,2-benzisoxazolyl, benzoxazolyl, benzothiazolyl, purinyl, pyridinyl,
20 dipyridyl, phenylpyridinyl, benzylpyridinyl, pyrimidinyl, phenylpyrimidinyl, pyrazinyl, 1,3,5-triazinyl, quinolinyl, phthalazinyl, quinazolinyl, and quinoxalinyl; or a carbocyclic group derived from phenyl, naphthyl, tolulyl, xylene, indenyl, stilbenyl, terphenyl, diphenylethylenyl, phenyl-cyclohexenyl, acenaphthylenyl, and anthracenyl, biphenyl, bibenzyl and related bibenzyl homologues represented by the formula (bb),

30



where n is a number from 1 to 8.

"Assay kit" means an assemblage of two cooperative elements, namely, (i) a wellplate apparatus, and (ii) biological assay materials.

5 "Biological assay materials" are materials necessary to conduct a biological evaluation of the efficacy of any library compound in a screen relevant to a selected disease state.

10 "Directed Library" is a collection of compounds created by a combinatorial chemistry process for the purpose of optimization of the activity of a lead compound, wherein each library compound has a common scaffold, and the library, considered in its entirety, is a collection of closely related homologues or analogues to the lead compound (compare to "Diverse library").

15 "Diverse library" means a library where the substituents on the combinatorial library scaffold are highly variable in constituent atoms, molecular weight, and structure and the library, considered in its entirety, is not a collection of closely related homologues or analogues
20 (compare to "Directed library").

"Electrophile" means an electron seeking reagent.

"Enone" means an α,β -unsaturated ketone.

25 "Lead compound" means a compound in a selected combinatorial library for which the Assay kit has revealed significant activity relevant to a selected disease state.

"Leaving group" means a group capable of substitution by a nucleophile.

30 "Library" is a collection of compounds created by a combinatorial chemical process, said compounds having a common pyrrolidine scaffold with one or more variable substituents.

"Library compound" means an individual reaction product (usually a single compound) in a library produced by the method of the invention.

"Parallel array synthesis" means a method of conducting combinatorial chemical synthesis of libraries wherein the individual combinatorial library reaction products are separately prepared and stored without prior or subsequent intentional mixing.

"Reaction zone" means the individual vessel location where the combinatorial chemical library compound preparation process of the invention is carried out and individual library compounds synthesized. Suitable reaction zones are the individual wells of a wellplate apparatus.

"Scaffold" means the invariant region (viz., pyrrolidine core) of the compounds which are members of a library.

"Simultaneous synthesis" means making of library of compounds within one production cycle of a combinatorial method (not making all library compounds at the same instant in time).

"Solid support" means a Wang resin in its hydroxyl or halogenated form. Wang resins are represented by the symbols, $\textcircled{\text{SS}}$ and \bullet , and are prepared as described in the article by Gui-shen Lu, referenced in the "Background of the Invention" section, supra.

"Substituents" are chemical radicals (excluding hydrogen) which are bonded to the scaffold through the combinatorial synthesis process. The different functional groups account for the diversity of molecules throughout the library and are selected to impart diversity of biological activity to the scaffold in the case of diverse libraries, and optimization of a particular biological activity in the case of directed libraries.

"Reagent" means a reactant, any chemical compound used in the combinatorial synthesis to place substituents on the scaffold of a library.

"Wellplate apparatus" means a structure capable of holding a plurality of library compounds in dimensionally fixed and defined positions.

"Ylide" means a species which in its ground state has charges of opposite sign on adjacent atoms.

"Non-interfering substituent" means those groups, other than hydrogen, that do not significantly impede the solid phase process of the invention and yield stable pyrrolidine library compounds. Suitable non-interfering radicals include, but are not limited to, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₁₀ alkoxy, C₇-C₁₂ aralkyl, C₇-C₁₂ alkaryl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, phenyl, substituted phenyl, toluyl, xylenyl, biphenyl, C₂-C₁₂ alkoxyalkyl, C₁-C₆ alkylsulfinyl, C₁-C₁₀ alkylsulfonyl, - (CH₂)_m-O-(C₁-C₁₀ alkyl), aryl, substituted aryl, substituted alkoxy, fluoroalkyl, aryloxyalkyl, heterocyclic radical, substituted heterocyclic radical, and nitroalkyl; where m is from 1 to 8. Preferred non-interfering radicals are C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₁-C₁₀ alkoxy, C₇-C₁₂ aralkyl, C₇-C₁₂ alkaryl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkenyl, phenyl, - (CH₂)_m-O-(C₁-C₁₀ alkyl), aryl, and substituted aryl.

"Aryl" means one or more aromatic rings, each of 5 or 6 carbon atoms. Multiple aryl rings may be fused, as in naphthyl, or unfused, as in biphenyl.

"Substituted Aryl" having one or more non-interfering groups as substituents.

"Halo" means chloro, fluoro, iodo or bromo.

"Heterocycle" means one or more rings of 5, 6, or 7 atoms with or without unsaturation or aromatic character and at least one ring atom which is not carbon. Preferred heteroatoms include sulfur, oxygen, and nitrogen. Multiple rings may be fused, as in quinoline or benzofuran.

"Substituted heterocycle" means heterocycle with one or more side chains formed from non-interfering substituents.

Selected Abbreviations used in this specification:

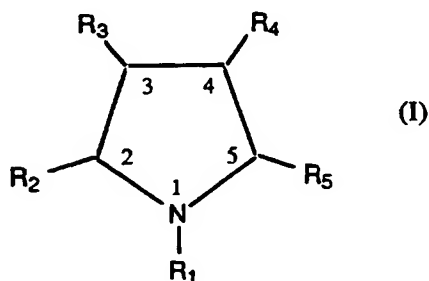
"DBU" - diazobicycloundecane

"TFA" - trifluoroacetic acid

"DMAP" - dimethyl amino pyridine

5 II. General description of the pyrrolidine combinatorial library:

The pyrrolidine library of the invention is a diverse combinatorial library comprising individual substituted pyrrolidine library compounds represented by the general
10 formula (I):



wherein;

15 the internal numbers in the pyrrolidine ring are used to denote substituent positions,

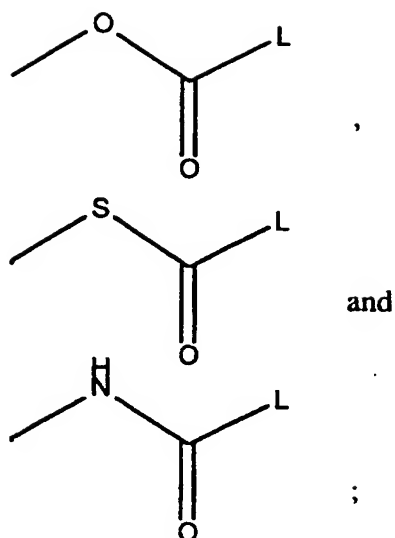
R₁ is an electrophilic group;

R₂ is a group represented by the formula:

20 $\text{---(L}_2\text{)---R}_6$

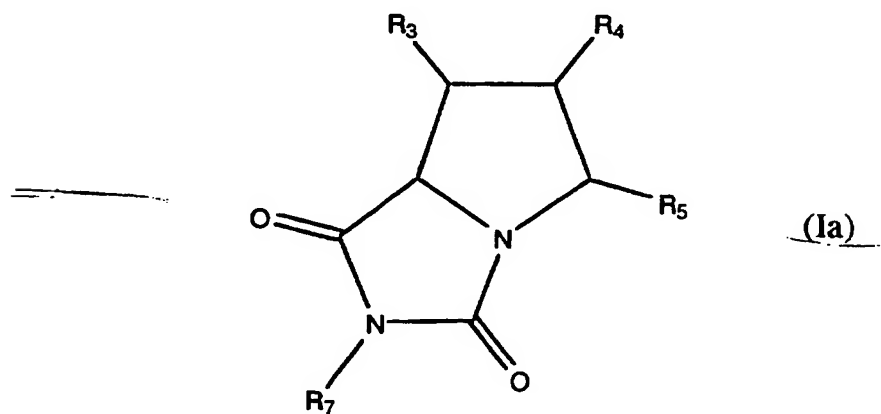
where divalent linking group -(L₂)- is selected from the group consisting of,

10



where "L" is the point of attachment of the pyrrolidine ring, and

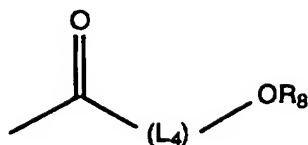
- 5 where R₆ is a non-interfering substituent, and R₁ and R₂ may join together to form a hydantoin ring on the pyrrolidone nucleus as represented by formula (Ia),



10

wherein R₇ is a non-interfering substituent;
 R₃ is an aromatic group;
 R₄ is a group of the general formula,

11



where $-(\text{L}_4)-$ is a divalent linking group, R_8 is hydrogen or a

non-interfering substituent; and

5 R_5 is an aromatic group.

The pyrrolidine library compounds of this invention are non-peptide, substantially non-naturally occurring molecules having a molecular weight range of from about 100 to about

10 700.

Preferred libraries contain pyrrolidine library compounds wherein;

R_1 is an electrophilic group derived from an electrophilic reagent having a molecular weight of from

15 about 30 to about 600 selected from the group consisting of; organic halides, acyl halides, sulfonic acid esters, organohaloformates, organosulfonyl halides, organic isocyanates, and organic isothiocyanates. Particularly useful electrophilic groups are those listed in Section III,

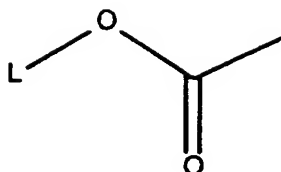
20 Step D, infra., of this specification. Other electrophilic groups for R_1 include, but are not limited to $\text{C}_1\text{-C}_{10}$ alkyl, $\text{C}_2\text{-C}_{10}$ alkenyl, $\text{C}_2\text{-C}_{10}$ alkynyl, $\text{C}_1\text{-C}_{10}$ alkoxy, $\text{C}_7\text{-C}_{12}$ aralkyl, $\text{C}_7\text{-C}_{12}$ alkaryl, $\text{C}_3\text{-C}_{10}$ cycloalkyl, $\text{C}_3\text{-C}_{10}$ cycloalkenyl, phenyl, substituted phenyl, toluy, xylenyl,

25 biphenyl, $\text{C}_2\text{-C}_{12}$ alkoxyalkyl, $\text{C}_1\text{-C}_6$ alkylsulfinyl, $\text{C}_1\text{-C}_{10}$ alkylsulfonyl, $-(\text{CH}_2)_m\text{-O-(C}_1\text{-C}_{10}\text{ alkyl)}$, aryl, substituted aryl, substituted alkoxy, fluoroalkyl, aryloxyalkyl, carbocyclic radical, substituted carbocyclic radical, heterocyclic radical, substituted heterocyclic radical, and

30 nitroalkyl; where m is from 1 to 8.

R_2 is a group wherein $-(\text{L}_2)-$ is,

12



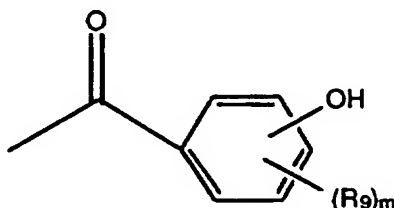
and R₆ is C₁ to C₁₀ alkyl; or

R₁ and R₂ may join together to form a hydantoin

wherein R₇ is C₁ to C₁₀ alkyl or an aromatic group;

5

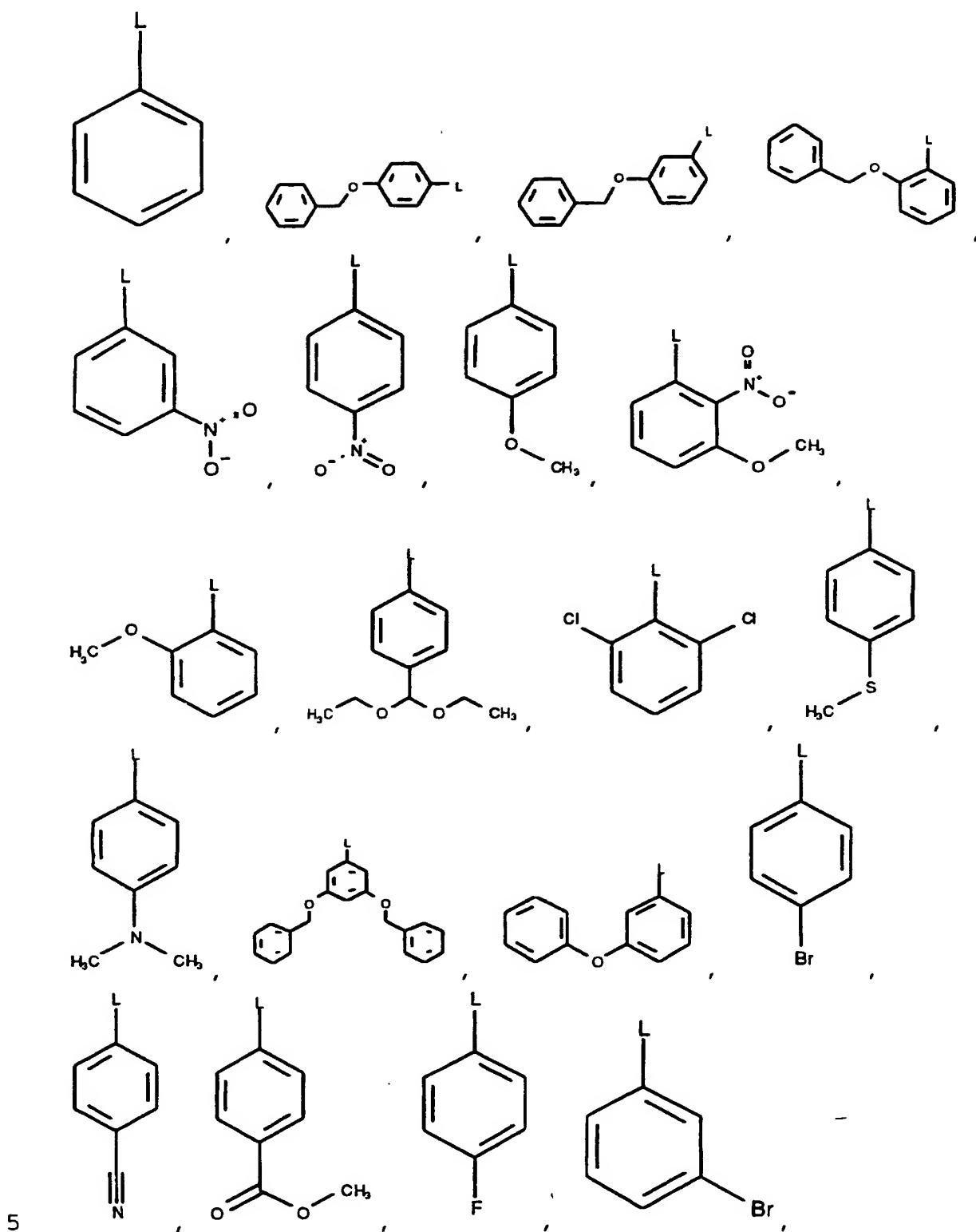
R₄ is preferably a group derived from the cleavage of the library compound from a Wang Resin, for example,



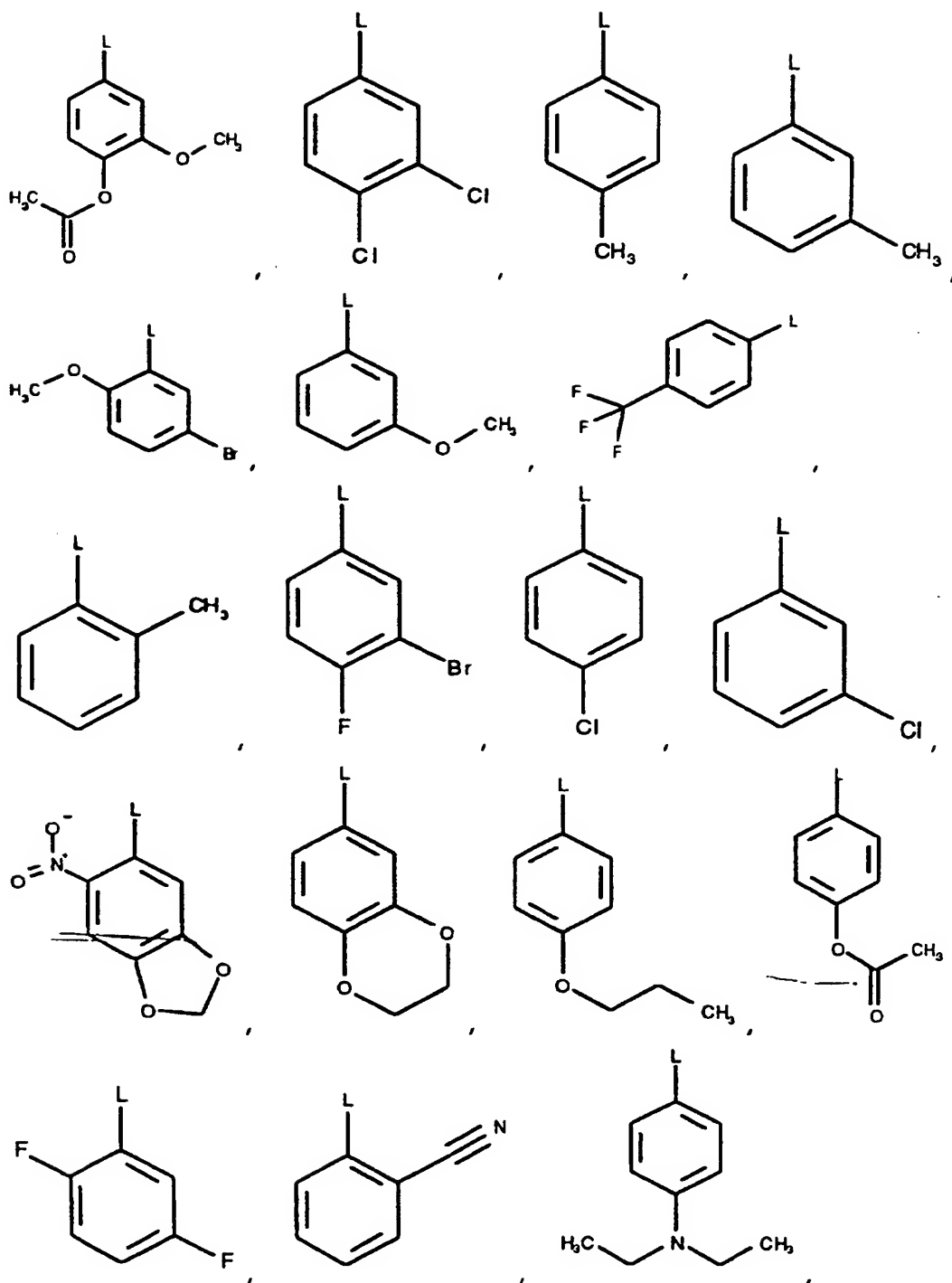
10 where R₉ is a non-interfering group and m is an integer from 0 to 3.

R₃ and R₅ are independently carbocyclic substituted or unsubstituted aromatic groups. Preferred groups for R₃, and

15 R₅ are selected from the following:

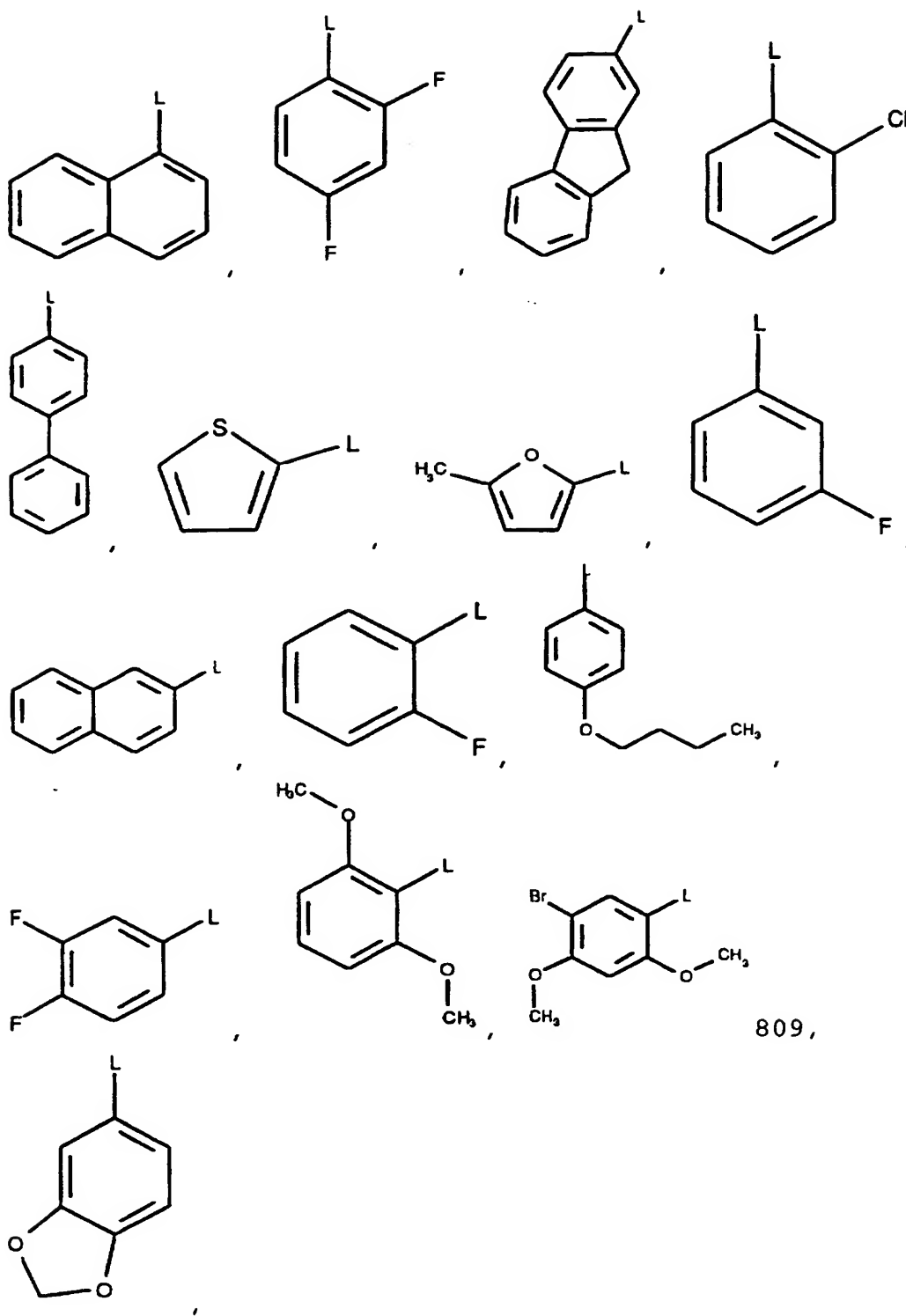


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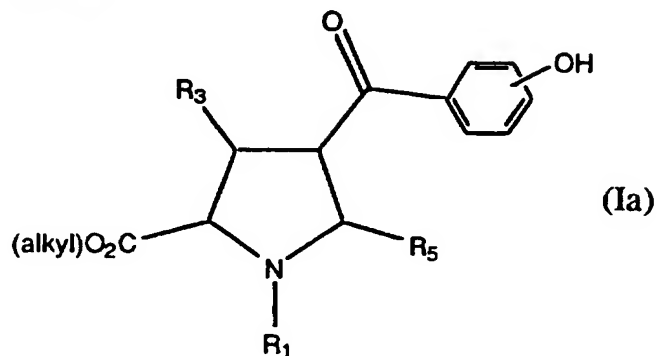
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where "L" is the point of attachment of the above electrophilic groups.

Preferred compounds of the invention are represented by
5 Formula (Ia) below:

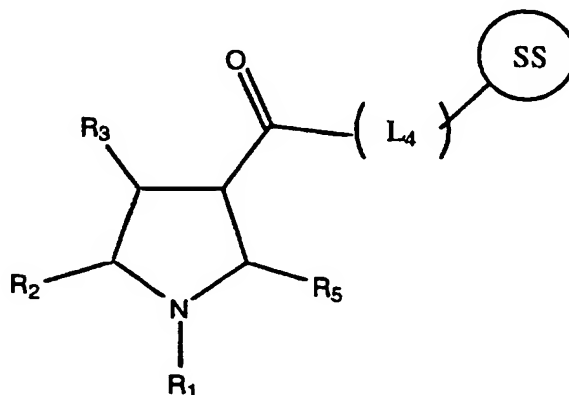


where R₁, R₃, and R₅ are as defined above.

10

III. Solid Support bound Pyrrolidine Library Compounds as Intermediates:

Products of this invention include libraries of intermediates, wherein said intermediates are the solid
15 supported form of the substituted pyrrolidine compounds of the invention. The intermediate library contains a plurality of diverse compounds, wherein each intermediate has the formula (X):



20

wherein;

R₁, R₂, R₃ and R₅ and -(L₄)- as previously defined and
as

SS

5 is a solid support.

IV. The Process for Making the Pyrrolidine Combinatorial
Library of the Invention:

Outline of Process Steps:

- 10 •Preparation of Starting Materials
- Step A - Methyl ketone functionalizing of the Wang
 resin solid support
- Step B - Aromatic enone formation
- Step C - 1,3-dipolar cycloaddition reaction with
15 azomethine ylide
- Step D - Electrophilic substitution of pyrrolidine
 nitrogen
- Step E - Library compound cleavage from solid support.

20 PROCESS STEP DETAILS

Preparation of Starting Materials:

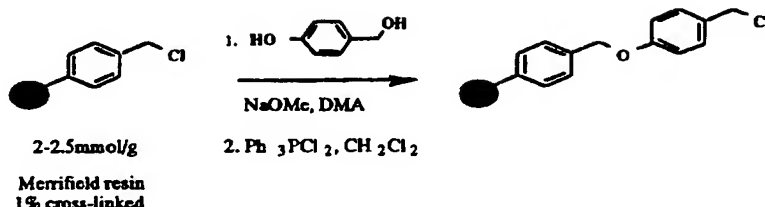
Starting Materials:

25

a) Preparation of the Solid Support --

The diverse highly functionalized pyrrolidine
combinatorial libraries of this invention are prepared by
solid phase reactions. A preferred solid support precursor
30 is a "Wang resin." The detailed preparation of a suitable
Wang resin for conducting the process in this invention is
set out in the "EXAMPLES" section, of this specification
infra., the disclosure of which is incorporated herein by

reference. Preparation of a Wang resin is illustrated in the following scheme:



Wang resins permit acid catalyzed cleavage in the final step of the process.

10 b) Preparation of the Azomethine Ylid Reagent

Azomethine ylids are prepared from aryl amino acid imines (See, Patzel, M. reference cited in the "Background of the Invention" section of this Disclosure). The aryl imines, may in term, be prepared from a condensation reaction of aryl aldehydes and amino acid esters or amides. Aryl imines prepared glycine are preferred in the practice of this invention.

The azomethine ylid reactant is itself prepared by condensation from aryl aldehydes and amino acid esters or amides.

General Pyrrolidine Library Process Making Details:

Reaction Medium - The reaction medium may be any liquid which is non-reactive with the reactants used in the library synthesis and is a non-solvent for the solid support. It is generally advantageous to have the nucleophilic reagent and electrophilic reagent soluble in the reaction medium.

Typical reaction media useful in the processes of the invention are methanol, chloroform, dimethylacetamide,

tetrahydrofuran, dimethylformamide, methylene chloride, and acetonitrile.

The Reaction Zone - the process of the invention may be carried out in any vessel capable of holding the liquid reaction medium and having inlet and outlet means. Preferably the process of the invention is carried out in containers adaptable to parallel array syntheses. Most preferably, the pyrrolidine library is formed in standard wellplates, such as the 96 well wellplate illustrated in Fig. 1 and/or the wellplate apparatus illustrated in Fig. 2. Each well may be filled by multiple delivery apparatus, automated or robotic apparatus, any of which may be either manually or computer controlled.

The diverse pyrrolidine library of this invention may take the form of a plurality of wellplates, each wellplate having wells containing a separate reaction product (library compound). In such cases, the library compounds are conveniently identified by their wellplate number and "x" column and "y" wellplate row coordinates.

A preferred technique for practicing the process of the invention is parallel array synthesis. With parallel array synthesis individual reaction products are prepared in each of multiple reaction zones. The amount of nucleophilic and electrophilic reagents reactants introduced into each reaction zone will depend on the desired amount of each library compound that is needed for conducting biological assays, archival storage and other related needs. Typically, the desired amount of individual reaction product is from 1 microgram to 50 milligrams.

The reaction zone is maintained at a temperature and for a time sufficient to permit substantial reaction of the solid phase pyrrolidine compound and the nucleophilic and electrophilic reagents.

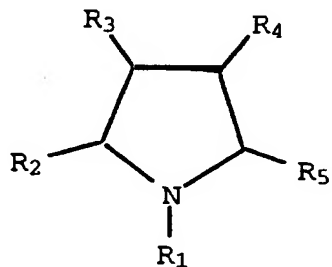
The time, temperature, and pressure of the combinatorial reaction zones used for the creation of

library compounds are not critical aspects of the invention. Reaction times for a single step of the reaction are generally from 0.1 seconds to 72 hours, with times of 1 hour to 24 hours being most often used. The temperature of the reaction may be any temperature between the freezing point and the boiling point of the liquid reaction medium, but is generally between -10°C and $+60^{\circ}\text{C}$, with 10°C to 40°C being preferred and ambient temperatures (about 20°C - 30°C) being most preferred. The reactions may be conducted at subatmospheric pressure or superatmospheric pressure (viz., 60Kg./m^2 - 21000 Kg./m^2 absolute), but ambient atmospheric pressure (about 10330 Kg./m^2 , absolute) is most often used.

Endpoint determination - The completion of the reaction may be determined by a number of conventional techniques. One method is to use thin layer chromatography.

Sequence of Operation - Within each process step the addition of the reactants to the reaction zone may take place in any order. For example, the solid supported reaction product may be initially added to the reaction zone followed by addition of the electrophilic or nucleophilic reagent, or vice versa.

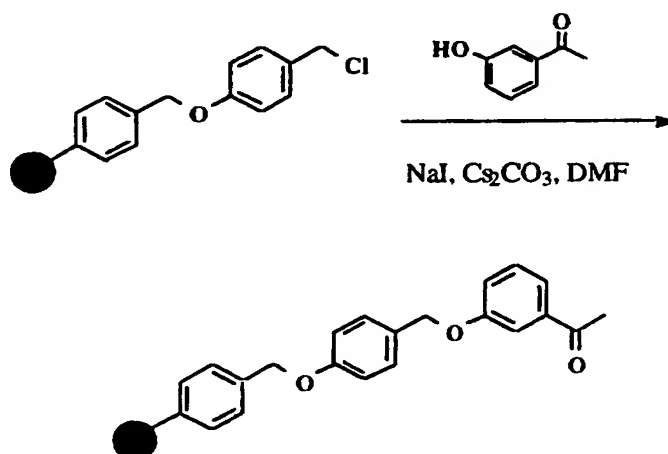
The principle sources for diversity in the library compounds of the invention are the groups R_1 , R_2 , R_3 and R_5 .



The groups R_2 and R_5 are provided in Step C of the process, the group R_1 is provided in Step D and the group R_3 is provided in Step B of the process.

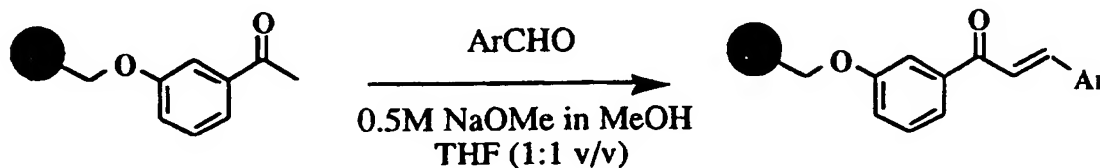
Step A.- Methyl ketone functionalizing of the Wang resin solid support

The solid support (viz., Wang resin) must first be functionalized with methyl ketone groups to permit enone formation later in the process of the invention. This is generally accomplished by reacting the solid support with a methyl ketone bearing compound. The solid support and the methyl ketone bearing compound must each have functionalities which permit reaction. For example, acetophenone may be reacted with a halogenated Wang resin as depicted by the following scheme:



Step B. - Aromatic Enone Formation:

The solid support reaction product of step A is reacted with an aromatic aldehyde as illustrated by the following scheme:



The aryl aldehyde is the source of molecular diversity for substituent R3 on the library compounds of the invention. The aromatic aldehyde may be selected from carbocyclic and heterocyclic aromatic nuclei having reactive aldehyde functionality.

Suitable aldehydes are;

- 2-fluorenecarboxaldehyde
- n-methylpyrrole-2-carboxaldehyde
- furfural
- 5-nitro-2-furaldehyde
- 5-methylfurfural
- 5-acetoxymethyl-2-furaldehyde
- 5-hydroxymethyl-2-furaldehyde
- benzaldehyde
- 2-bromobenzaldehyde
- 2-fluorobenzaldehyde
- pentafluorobenzaldehyde
- 2-chlorobenzaldehyde
- 2,4-dichlorobenzaldehyde
- 2-chloro-6-fluorobenzaldehyde
- 2,6-dichlorobenzaldehyde
- o-anisaldehyde
- 2,3-dimethoxybenzaldehyde
- 2,3,4-trimethoxybenzaldehyde
- 2,4-dimethoxybenzaldehyde
- 2,4,5-trimethoxybenzaldehyde
- 2,4,6-trimethoxybenzaldehyde
- 2,5-dimethoxybenzaldehyde
- 2-ethoxybenzaldehyde
- salicylaldehyde
- 3,5-dibromosalicylaldehyde
- 3-fluorosalicylaldehyde
- 3,5-dichlorosalicylaldehyde
- 3,5-diiodosalicylaldehyde
- 3-ethoxysalicylaldehyde

- 2,3-dihydroxybenzaldehyde
2,3,4-trihydroxybenzaldehyde
4-(diethylamino)salicylaldehyde
2-hydroxy-4-methoxybenzaldehyde
5 4,6-dimethoxy-2-hydroxybenzaldehyde
2,4,6-trihydroxybenzaldehyde
5-bromosalicylaldehyde
5-chlorosalicylaldehyde
2-hydroxy-5-methoxybenzaldehyde
10 2,5-dihydroxybenzaldehyde
2-carboxybenzaldehyde
2-(trifluoromethyl)benzaldehyde
o-tolualdehyde
2,3-dimethyl-p-anisaldehyde
15 2,4-dimethylbenzaldehyde
mesitaldehyde
2,5-dimethylbenzaldehyde
2,5-dimethyl-p-anisaldehyde
3-cyanobenzaldehyde
20 3-bromobenzaldehyde
3-bromo-4,5-dimethoxybenzaldehyde
5-bromo-2-methoxybenzaldehyde
3-fluorobenzaldehyde
3-fluoro-p-anisaldehyde
25 3-chlorobenzaldehyde
3,4-dichlorobenzaldehyde
3,5-dichlorobenzaldehyde
3-phenoxybenzaldehyde
3-(3,4-dichlorophenoxy)benzaldehyde
30 3-(3,5-dichlorophenoxy)benzaldehyde
3-(3-(trifluoromethyl)phenoxy)benzaldehyde
3-(4-chlorophenoxy)benzaldehyde
3-(4-methoxyphenoxy)benzaldehyde
3-(4-tert-butylphenoxy)benzaldehyde
35 3-(4-methylphenoxy)benzaldehyde

- m-anisaldehyde
4-acetoxy-3-methoxybenzaldehyde
3,4-dimethoxybenzaldehyde
3,4,5-trimethoxybenzaldehyde
5 4-benzyloxy-3-methoxybenzaldehyde
3,5-dimethoxybenzaldehyde
3-benzyloxybenzaldehyde
3-hydroxybenzaldehyde
3-hydroxy-4-methoxybenzaldehyde
10 3,4-dihydroxybenzaldehyde
3,4,5-trihydroxy benzaldehyde
3-(trifluoromethyl)benzaldehyde
m-tolualdehyde
3-methyl-p-anisaldehyde
15 4-cyanobenzaldehyde
4-bromobenzaldehyde
4-fluorobenzaldehyde
4-chlorobenzaldehyde
4-acetamidobenzaldehyde
20 4-dimethylaminobenzaldehyde
4-diethylaminobenzaldehyde
4-phenoxybenzaldehyde
4-acetoxybenzaldehyde
p-anisaldehyde
25 3-benzyloxy-4-methoxybenzaldehyde
4-benzyloxybenzaldehyde
4-ethoxybenzaldehyde
4-n-butoxybenzaldehyde
1-naphthaldehyde
30 2-methoxy-1-naphthaldehyde
2-hydroxy-1-naphthaldehyde
4-methoxy-1-naphthaldehyde
2-naphthaldehyde
1-pyrenecarboxaldehyde
35 3,4-dibenzyloxybenzaldehyde

- n-ethyl-3-carbazolecarboxaldehyde
2-methyl-9-acridinecarboxaldehyde
pyrrole-2-carboxaldehyde
2-thiophenecarboxaldehyde
5 3-methylthiophene-2-carboxaldehyde
4-bromothiophene-2-aldehyde
5-bromo-2-thiophenecarboxaldehyde
5-nitrothiophene-2-carboxaldehyde
5-methyl-2-thiophenecarboxaldehyde
10 3-thiophenecarboxaldehyde
indole-3-carboxaldehyde
5-methoxyindole-3-carboxaldehyde
piperonal
6-nitropiperonal
15 2-pyridinecarboxaldehyde
6-methyl-2-pyridinecarboxaldehyde
3-pyridinecarboxaldehyde
4-pyridinecarboxaldehyde
3-quinolinecarboxaldehyde
20 4-quinolinecarboxaldehyde
4-hydroxybenzaldehyde
3-ethoxy-4-hydroxybenzaldehyde
3,5-dimethyl-4-hydroxybenzaldehyde
~~4-biphenylcarboxaldehyde~~
25 4-(methylthio)benzaldehyde
methyl 4-formylbenzoate
4-carboxybenzaldehyde
4-trifluoromethylbenzaldehyde
4-isopropylbenzaldehyde
30 p-tolualdehyde
4-ethylbenzaldehyde
4-chloro-3-nitrobenzaldehyde
3,5-dinitro-2-hydroxybenzaldehyde
3-hydroxy-4-nitrobenzaldehyde
35 4-hydroxy-3-nitrobenzaldehyde

- 5-nitrovanillin
2-nitrobenzaldehyde
2,6-dinitrobenzaldehyde
6-nitroveratraldehyde
5 3-methoxy-2-nitrobenzaldehyde
2-chloro-6-nitrobenzaldehyde
3-nitrobenzaldehyde
5-chloro-2-nitrobenzaldehyde
2-chloro-5-nitrobenzaldehyde
10 5-hydroxy-2-nitrobenzaldehyde
5-nitrosalicylaldehyde
4-nitrobenzaldehyde
1,4-benzodioxan-6-carboxaldehyde
2,3-dichlorobenzaldehyde
15 3-ethoxy-4-methoxybenzaldehyde
3,5-bis(trifluoromethyl)benzaldehyde
2,3,6-trichlorobenzaldehyde
terephthalaldehyde monodiethylacetal
2,3-difluorobenzaldehyde
20 2,6-difluorobenzaldehyde
2,4-difluorobenzaldehyde
2,5-difluorobenzaldehyde
3,4-difluorobenzaldehyde
3,5-difluorobenzaldehyde
25 4-dimethylamino-1-naphthaldehyde
3-furaldehyde
3,4-dimethoxy-5-hydroxybenzaldehyde
2,3,5-trichlorobenzaldehyde
2,6-dimethoxybenzaldehyde
30 5-bromo-2,4-dimethoxybenzaldehyde
2,4-dimethoxy-3-methylbenzaldehyde
4-stilbenecarboxaldehyde
4-(3-dimethylaminopropoxy)benzaldehyde
2,4-dihydroxybenzaldehyde
35 3-chloro-4-fluorobenzaldehyde

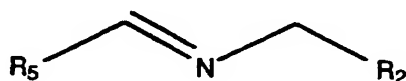
- 2-methylindole-3-carboxaldehyde
4-hydroxy-3-methylbenzaldehyde
2-(diphenylphosphino)benzaldehyde
2,4-dinitrobenzaldehyde
5 4-n-propoxybenzaldehyde
1-methylindole-3-carboxaldehyde
5-bromo-2-hydroxy-3-methoxybenzaldehyde
3-bromo-4-methoxybenzaldehyde
4-acetoxy-3,5-dimethoxybenzaldehyde
10 3,5-dihydroxybenzaldehyde
3-methoxy-4-(4-nitrobenzyloxy)benzaldehyde
2,3-(methylenedioxy)benzaldehyde
2-hydroxy-3-methoxy-5-nitrobenzaldehyde
2-cyanobenzaldehyde
15 5-ethyl-2-furaldehyde
4-tert-butylbenzaldehyde
3-tetrafluoroethoxybenzaldehyde
3-carboxybenzaldehyde
1-acetyl-3-indolecarboxaldehyde
20 4-(trifluoromethoxy)benzaldehyde
3-bromo-4-fluorobenzaldehyde
3-(trifluoromethoxy)benzaldehyde
2-chloro-4-fluorobenzaldehyde
5-(3-nitrophenyl)furfural
25 2-chloro-4-hydroxybenzaldehyde
2,3,4-trifluorobenzaldehyde
2-fluoro-3-(trifluoromethyl)benzaldehyde
2-fluoro-6-(trifluoromethyl)benzaldehyde
4-fluoro-2-(trifluoromethyl)benzaldehyde
30 4-(dibutylamino)benzaldehyde
5-(trifluoromethoxy)salicylaldehyde
3-fluoro-2-methylbenzaldehyde
3,5-dibenzyloxybenzaldehyde
5-(4-nitrophenyl)furfural
35 2-chloro-3-quinolinecarboxaldehyde

- 2-chloro-5-(trifluoromethyl)benzaldehyde
5-bromo-2-furaldehyde
2,3,5,6-tetrafluorobenzaldehyde
4-methyl-5-imidazolecarboxaldehyde
5 2-benzyloxy-4,5-dimethoxybenzaldehyde
3,5-di-tert-butyl-2-hydroxybenzaldehyde
2,4-diethoxy-m-tolualdehyde
4-tert-pentylbenzaldehyde

- 10 Alternatively, aldehyde derivative of the radicals depicted in the preceding section II, definition of R₃ and R₅ may be used as the aromatic aldehyde reactant.

- 15 Step C. - 1,3-dipolar cycloaddition reaction with azomethine ylide

The azomethine ylid reactant has the following formula;



- 20 where R₅ and R₂ are as defined above.

R₅ is an aromatic group and R₂ is an amino acid ester or amide.

- 25 The azomethine ylid reactant is the source for diversity in the R₂ and R₃ substituents of pyrrolidines represented by Formula I, supra.

- 30 The solid supported reaction product of step B is reacted with an aryl imine of an amino acid ester or an amide analog thereof. The aryl imine reactant is itself prepared by condensation of aryl aldehydes and amino acid esters or amides.

This reaction is further illustrated by the reaction scheme set out below:

29

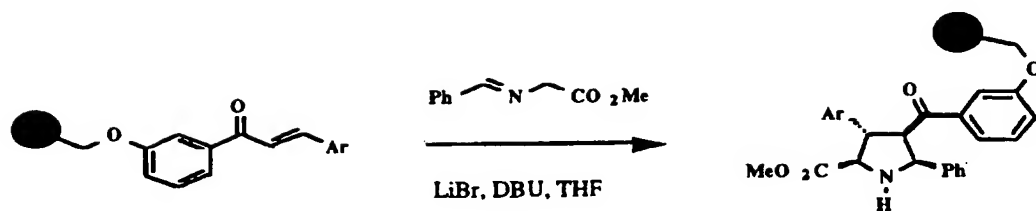
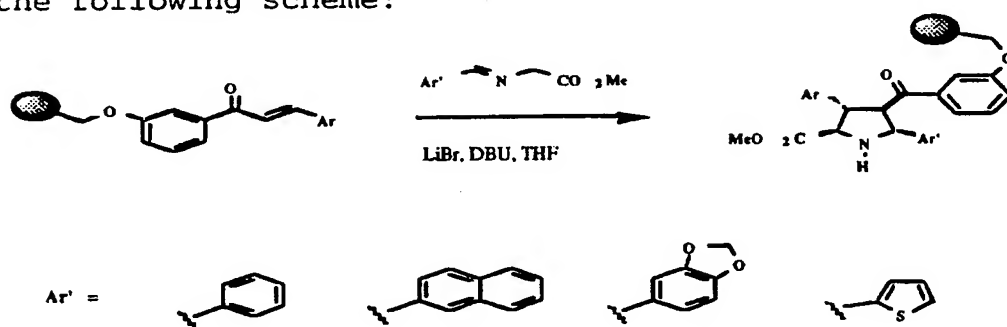
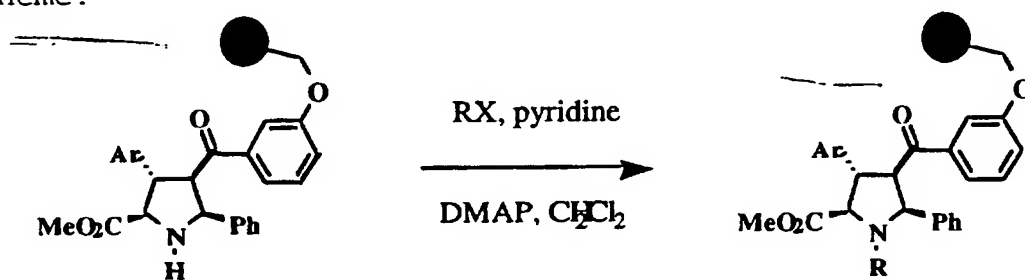


Illustration of the use of alternative imines is shown
5 in the following scheme:



Step D - Electrophilic substitution of pyrrolidine nitrogen

The product of Step C is reacted with an electrophile.
10 The electrophile reacts with the nitrogen atom on the
pyrrolidine nitrogen ring. Alkylation and acylation
reactions are suitable, for example, as show the following
scheme:



15

Electrophilic reactants suitable for use in this step
have a molecular weight of from about 15 to 600 and are
selected from organic halides, acyl halides, sulfonic acid
esters, organohaloformates, organosulfonylhalides, organic
20 isocyanates, and organic isothiocyanates.

Suitable electrophilic reagents for practice of this process step of the invention are set out below:

Acyl Halides --

- 5 3,5-bis(trifluoromethyl)benzoyl chloride
- benzoyl chloride
- 2-bromobenzoyl chloride
- 2-fluorobenzoyl chloride
- pentafluorobenzoyl chloride
- 2,4-difluorobenzoyl chloride
- 10 2,6-difluorobenzoyl chloride
- 2-chlorobenzoyl chloride
- 2,4-dichlorobenzoyl chloride
- 2,6-dichlorobenzoyl chloride
- o-acetylsalicyloyl chloride
- 15 2-methoxybenzoyl chloride
- 2,6-dimethoxybenzoyl chloride
- 2-(trifluoromethyl)benzoyl chloride
- o-toluoyl chloride
- 3-bromobenzoyl chloride
- 20 3-fluorobenzoyl chloride
- 3-chlorobenzoyl chloride
- 3,4-dichlorobenzoyl chloride
- m-anisoyl chloride
- 3,4-dimethoxybenzoyl chloride
- 25 3,4,5-trimethoxybenzoyl chloride
- 3,5-dimethoxybenzoyl chloride
- 3-ethoxybenzoyl chloride
- isophthaloyl chloride
- trimesoyl chloride
- 30 3-(trifluoromethyl)benzoyl chloride
- m-toluoyl chloride
- 3-(chloromethyl) benzoyl chloride
- 4-bromobenzoyl chloride
- 4-fluorobenzoyl chloride
- 35 4-chlorobenzoyl chloride

- p-anisoyl chloride
4-ethoxybenzoyl chloride
4-n-butoxybenzoyl chloride
4-n-hexyloxybenzoyl chloride
5 4-heptyloxybenzoyl chloride
4-biphenylcarbonyl chloride
terephthaloyl chloride
4-(trifluoromethyl)benzoyl chloride
4-tert-butylbenzoyl chloride
10 p-toluoyl chloride
4-ethylbenzoyl chloride
4-n-propylbenzoyl chloride
4-butylbenzoyl chloride
4-pentylbenzoyl chloride
15 4-hexylbenzoyl chloride
4-n-heptylbenzoyl chloride
methyl oxalyl chloride
ethyl oxalyl chloride
heptafluorobutyryl chloride
20 2-acetoxyisobutyryl chloride
pivaloyl chloride
3-chloropivaloyl chloride
2-bromopropionyl chloride
2,3-dibromopropionyl chloride
25 2,3-dichloropropionyl chloride
o-acetylmandelic acid chloride
itaconyl chloride
methacryloyl chloride
isobutyryl chloride
30 2-ethylhexanoyl chloride
acetyl chloride
bromoacetyl chloride
chloroacetyl chloride
phenoxyacetyl chloride
35 4-chlorophenoxyacetyl chloride

- methoxyacetyl chloride
phenylacetyl chloride
3,3-dimethylacryloyl chloride
cinnamoyl chloride
5 fumaryl chloride
ethyl malonyl chloride
tert-butylacetyl chloride
isovaleryl chloride
undecanoyl chloride
10 lauroyl chloride
myristoyl chloride
palmitoyl chloride
heptadecanoyl chloride
stearoyl chloride
15 propionyl chloride
3-bromopropionyl chloride
3-chloropropionyl chloride
hydrocinnamoyl chloride
succinyl chloride
20 3-carbomethoxypropionyl chloride
ethyl succinyl chloride
butyryl chloride
4-bromobutyryl chloride
4-chlorobutyryl chloride
25 valeryl chloride
5-chlorovaleryl chloride
adipoyl chloride
hexanoyl chloride
6-bromohexanoyl chloride
30 pimeloyl chloride
heptanoyl chloride
suberoyl chloride
octanoyl chloride
10-undecenoyl chloride
35 2-chloro-2,2-diphenylacetyl chloride

- dichloroacetyl chloride
alpha-chlorophenylacetyl chloride
2-chloropropionyl chloride
2-iodobenzoyl chloride
5 4-iodobenzoyl chloride
cyclopropanecarbonyl chloride
trans-2-phenyl-1-cyclopropanecarbonyl chloride
cyclobutanecarbonyl chloride
cyclopentanecarbonyl chloride
10 3-cyclopentylpropionyl chloride
cyclohexanecarbonyl chloride
4-cyanobenzoyl chloride
2-furoyl chloride
1-naphthoyl chloride
15 2-naphthoyl chloride
pyrrolidine-2-carbonyl chloride
2-thiopheneacetyl chloride
trimellitic anhydride chloride
2,6-pyridinedicarboxylic acid chloride
20 2-quinoxaloyl chloride
2-nitrobenzoyl chloride
3-nitrobenzoyl chloride
3,5-dinitrobenzoyl chloride
4-nitrobenzoyl chloride
25 3,4-dimethoxyphenylacetyl chloride
3-methyladipoyl chloride
3,5-dichlorobenzoyl chloride
2,5-difluorobenzoyl chloride
3,4-difluorobenzoyl chloride
30 9-fluorenone-4-carbonyl chloride
3,5-difluorobenzoyl chloride
(s)-(-)-n-(trifluoroacetyl)prolyl chloride
benzyloxyacetyl chloride
acetoxycetyl chloride
35 3-cyanobenzoyl chloride

- 2,5-dimethoxyphenylacetyl chloride
3-methoxyphenylacetyl chloride
iminodibenzyl-5-carbonyl chloride
2,4,6-trimethylbenzoyl chloride
5 tetrafluorosuccinyl chloride
perfluorooctanoyl chloride
diphenylacetyl chloride
alpha-methyl valeroyl chloride
methyl malonyl chloride
10 ethyl glutaryl chloride
5-bromovaleryl chloride
methyl adipyl chloride
3-cyclohexenecarbonyl chloride
3-isocyanato benzoyl chloride
15 2,4,6-triisopropylbenzoyl chloride
fluoroacetyl chloride
2-ethoxybenzoyl chloride
piperonyloyl chloride
2,4-dimethoxybenzoyl chloride
20 2,3,5,6-tetrachloroterephthaloyl chloride
5-(dimethylsulfamoyl)-2-methoxybenzoyl chloride
2-(4-chlorobenzoyl)benzoyl chloride
2,2-bis(chloromethyl)propionyl chloride
cinnamylidenemalonyl chloride
25 2-phenoxypropionyl chloride
2-phenylbutyryl chloride
2-ethylbutyryl chloride
p-tolylacetyl chloride
gamma-methylvaleroyl chloride
30 3,3-dichloropivaloyl chloride
1-methyl-1-cyclohexanecarboxylic acid chloride
2-(2,4,5-trichlorophenoxy)acetyl chloride
4-chloro-3-nitrobenzoyl chloride
4-methyl-3-nitrobenzoyl chloride
35 2,3-dichlorobenzoyl chloride

- morpholine-4-carbonyl chloride
p-chlorophenylacetyl chloride
bicyclo[2.2.1]heptane-2-carbonyl chloride
d(-)-alpha-formyloxy-alpha-phenylacetyl chloride
5 d(-)-alpha-phenylglycine chloride hydrochloride
trifluoroacetyl chloride
pentafluoropropionyl chloride
hexafluoroglutaryl chloride
2-chlorocinnamoyl chloride
10 o-methoxycinnamyl chloride
5-nitro-2-furoyl chloride
2-chlorobutyryl chloride
4-phenylazobenzoyl chloride
4-n-amyloxybenzoyl chloride
15 4-decylbenzoyl chloride
4-octylbenzoyl chloride
dl-2-methylbutyryl chloride
linolenoyl chloride
linolelaidoyl chloride
20 11h-eicosafluoroundecanoyl chloride
9h-hexadecafluorononanoyl chloride
2,3-difluorobenzoyl chloride
2-(benzoyloxymethyl)benzoyl chloride
2,2-dimethylvaleroyl chloride
25 3,5,5-trimethylhexanoyl chloride
phenothiazine-10-carbonyl chloride
3,4-dimethyl benzoyl chloride
(+)-p-(2-methylbutyl)benzoyl chloride
2,4-dichlorophenoxyacetic chloride
30 pentadecanoyl chloride
nonadecanoyl chloride
neoheptanoyl chloride
9-anthracenecarbonyl chloride
2-ethoxy-1-naphthoyl chloride
35 pyrrolidine carbonyl chloride

- m-(chlorosulfonyl)benzoyl chloride
2-n-propyl-n-valeroyl chloride
2-chloro-4-nitrobenzoyl chloride
2-phenoxybutyryl chloride
5 2-chloronicotinyl chloride
6-chloronicotinyl chloride
4-(trifluoromethoxy)benzoyl chloride
2-(trifluoromethoxy)benzoyl chloride
2,6-dichloropyridine-4-carbonyl chloride
10 3-chlorobenzo[b]pyrrolidine-2-carbonyl chloride
4-chloromethylbenzoyl chloride
neodecanoyl chloride
(phenylthio)acetyl chloride
4-carbethoxyhexafluorobutyryl chloride
15 octafluoroadipoyl chloride
2-diazo-3,3,3-trifluoropropionyl chloride
2-bromobutyryl chloride
arachidoyl chloride
cis-vaccenoyl chloride
20 11-eicosenoyl chloride
behenoyl chloride
petroselinoyl chloride
palmitoleoyl chloride
tridecanoyl chloride
25 2-chloro-5-nitrobenzoyl chloride
3-methylthiopropionyl chloride
methyl 4-chlorocarbonylbenzoate
anthraquinone-2-carbonyl chloride
carbazole-n-carbonyl chloride
30 2-nitrophenoxyacetyl chloride
2-bromo-2-methylpropionyl chloride
2-fluoro-3-(trifluoromethyl)benzoyl chloride
2-fluoro-4-(trifluoromethyl)benzoyl chloride
2-fluoro-5-(trifluoromethyl)benzoyl chloride
35 3-fluoro-5-(trifluoromethyl)benzoyl chloride

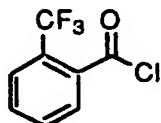
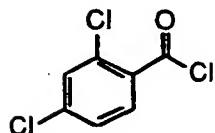
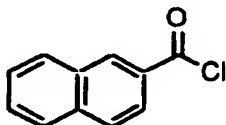
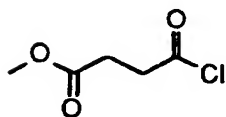
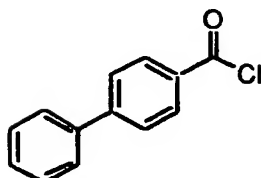
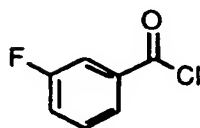
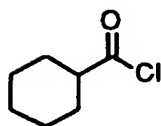
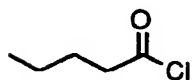
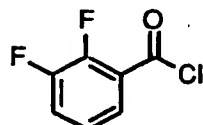
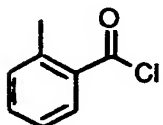
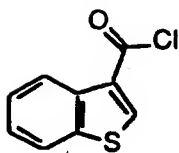
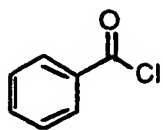
- 4-fluoro-2-(trifluoromethyl)benzoyl chloride
4-fluoro-3-(trifluoromethyl)benzoyl chloride
2-fluoro-6-(trifluoromethyl)benzoyl chloride
2,3,6-trifluorobenzoyl chloride
5 2,4,5-trifluorobenzoyl chloride
2,4-di(trifluoromethyl)benzoyl chloride
2,6-di(trifluoromethyl)benzoyl chloride
3-(trifluoromethoxy)benzoyl chloride
m-(fluorosulfonyl)benzoyl chloride
10 trans-1,2-cyclobutanedicarboxylic acid chloride
3-cyclohexylpropionyl chloride
4-ethyl-2,3-dioxo-1-piperazinecarbonylchloride
isoxazole-5-carbonyl chloride
bromodifluoroacetyl chloride
15 erucoyl chloride
2,4,6-trifluorobenzoyl chloride
dichlorochrysanthemic acid chloride
isononanoyl chloride
1-adamantanecarbonyl chloride
20 2,5-bis(trifluoromethyl)benzoyl chloride
2,3,4-trifluorobenzoyl chloride
2,3,4,5-tetrafluorobenzoyl chloride
2,4,6-trichlorobenzoyl chloride
2,4-dichloro-5-fluorobenzoyl chloride
25 4-methoxyphenylacetyl chloride
trans-3-(trifluoromethyl)cinnamoyl chloride
3-(dichloromethyl) benzoyl chloride
4-isocyanato benzoyl chloride
heneicosanoyl chloride
30 2-chloroisobutyryl chloride
trans-4-nitrocinnamoyl chloride
3,4,5-trifluorobenzoyl chloride
5-fluoro-2-(trifluoromethyl)benzoyl chloride
2,3,5-trifluorobenzoyl chloride
35 2-chloro-4-fluorobenzoyl chloride

- (-)-alpha-chlorophenylacetyl chloride
- 2-(para-tolylsulfonyl)acetyl chloride
- 4-methyl-4-nitrohexanoyl chloride
- 1-chloro-4-fluorosulfonyl-2-naphthoyl chloride
- 5 2,3-dibromo-3-phenylpropionyl chloride
- 2-menthoxyacetyl chloride
- 2-phenyl-2-(phenylsulfonyl)acetyl chloride
- 4,4,4-trifluorocrotonyl chloride
- 4,4,4-trifluorobutyryl chloride
- 10 3,4-dichloro-2,5-thiophenedicarbonyl chloride
- pentachlorobenzoyl chloride
- 4,4,7,7-tetranitrosebacoyl chloride
- alpha,alpha'-dimethylsuccinyl chloride
- alpha-bromoisovaleryl chloride
- 15 benzoyl chloride
- oleoyl chloride
- methyl suberyl chloride
- gamma-linolenoyl chloride
- (-)-camphanic acid chloride
- 20 4,4'-stilbenedicarbonyl chloride
- chlorinated benzoyl chloride
- (1r)-(+)-camphanic chloride
- 2-(4-nitrophenoxy)tetradecanoyl chloride
- 7-[(chlorocarbonyl)methoxy]-4-methylcoumarin
- 25 n,n-bis(2-chloroethyl)carbamoyl chloride
- (s)-(-)-2-acetoxypropionyl chloride
- linoleoyl chloride
- 3-chlorotetrafluoropropionyl chloride
- 3,4-dichloropentafluorobutyryl chloride
- 30 7h-dodecafluoroheptanoyl chloride
- 5h-octafluoropentanoyl chloride
- perfluorononanoyl chloride
- 3h-tetrafluoropropionyl chloride
- 2-bromo-2,3,3,3-tetrafluoropropanoyl chloride
- 35 arachidonoyl chloride

- pentachloropropionyl chloride
4-decenoyl chloride
tridecafluoroheptanoyl chloride
undecafluorocyclohexanecarbonyl chloride
5 4-n-nonylbenzoyl chloride
3-(trichlorogermyl)propionylchloride
3,4,5-triiodobenzoyl chloride
2-(phenylthio)propionyl chloride
2,2,2-triphenylacetyl chloride
10 d(-)-alpha-azido-phenyl acetyl chloride
4-azido-benzoyl chloride
difluoroacetyl chloride
5-chloropyrazine-2-carbonyl chloride
n-(1-naphthalenesulfonyl)-1-phenylalanyl chloride
15 n-(4-nitrophenylsulfonyl)-1-phenylalanyl chloride
n-(p-toluenesulfonyl)-1-phenylalanyl chloride
dimethylmalonyl chloride
methyl sebacoyl chloride
2,5-dichloropyridine-3-carbonyl chloride
20 3-(2,5 xylyloxy) propionyl chloride.

Additionally, acyl chorides suitable for use in the process of the invention are represented by the following formulae:

40



Organic Halides --

benzyl bromide

5

alpha-bromo-o-xylene

alpha-bromo-m-xylene

4-(tert-butyl)benzyl bromide

alpha-bromo-p-xylene

tert-butyl bromoacetate

10

methyl bromoacetate

benzyl bromoacetate

ethyl bromoacetate

- 2-bromoacetophenone
2-bromo-2'-methoxyacetophenone
2-bromo-2',4'-dimethoxyacetophenone
2-bromo-2',5'-dimethoxyacetophenone
5 3-methoxyphenacyl bromide
2-bromo-4'-methoxyacetophenone
2-bromo-4'-phenylacetophenone
2-bromo-4'-methylacetophenone
ethyl bromopyruvate
10 1-bromopinacolone
1-bromo-2-butanone
1-bromo-2,2-dimethoxypropane
1-bromo-2,2-dimethylpropane
bromoacetaldehyde dimethyl acetal
15 bromoacetaldehyde diethyl acetal
1-bromo-2-methylpropane
1-bromo-2-ethylbutane
2-ethylhexyl bromide
1-bromodecane
20 1-bromoundecane
2-bromoacetamide
iodoacetamide
4-(bromomethyl)phenylacetic acid phenacyl ester
isopropyl bromoacetate
25 5-bromo-2-methyl-2-pentene
3,4-difluorobenzyl bromide
2,5-difluorobenzyl bromide
3,5-bis(trifluoromethyl)benzyl bromide
2-bromo-2'-nitroacetophenone
30 3,5-difluorobenzyl bromide
2,4-bis(trifluoromethyl)benzyl bromide
8-bromo-1-octanol
4-(bromomethyl)phenylacetic acid
methyl (r)-(+) -3-bromo-2-methylpropionate
35 4-iodobutyl acetate

- 7-acetoxy-4-bromomethylcoumarin
4-bromomethyl-6,7-dimethoxycoumarin
2,4-difluorobenzyl bromide
methyl 2-(bromomethyl)acrylate
5 3-bromopropionaldehyde dimethyl acetal
(r)-(-)-3-bromo-2-methyl-1-propanol

Sulfonic Acid Esters --

- ethyl trifluoromethanesulfonate
10 2,2,2-trifluoroethyl p-toluenesulfonate
2-chloroethyl-p-toluenesulfonate
1,3-propane sultone
5'-tosyladenosine
1,4-butane sultone
15 cyanomethyl benzenesulfonate
hexadecyl methanesulfonate
ethyl methanesulfonate
2-chloroethyl methanesulfonate
ethyl p-toluenesulfonate
20 trans-2-hydroxycyclohexyl p-toluenesulfonate
(2r)-(-)-glycidyl tosylate
(s)-(+)-2-methylbutyl methanesulfonate
(s)-(+)-2-methylbutyl p-toluenesulfonate
(s)-(+)-1-phenyl-1,2-ethanediol 2-tosylate
25 (2r)-(-)-glycidyl 3-nitrobenzenesulfonate
propargyl benzenesulfonate
2,2-dimethyl-1,3-dioxolan-4-ylmethyl p-toluenesulfonate
(r)-(-)-2,2-dimethyl-1,3-dioxolan-4-ylmethyl p-
toluenesulfonate
30 (s)-(+)-2,2-dimethyl-1,3-dioxolan-4-ylmethyl p-
toluenesulfonate
1,2:5,6-di-o-isopropylidene-3-o-(methylsulfonyl)-alpha-
d-glucofuranose
ethyl 1-2-((methylsulfonyl)oxy)propionate
35 (2s)-(+)-glycidyl tosylate

- (2s)-(+)-glycidyl 3-nitrobenzenesulfonate
3-o-acetyl-6-o-benzoyl-5-o-(methylsulfonyl)-1,2-o-
isopropylidene-alpha-d-glucofu
(r)-(-)-1-benzyloxy-3-(p-tosyloxy)-2-propanol
5 (s)-(+)-1-benzyloxy-3-(p-tosyloxy)-2-propanol
ethyl 1-2-((trifluoromethylsulfonyl)oxy)propionate
2-(2-chloroethoxy)ethyl methanesulfonate
1-cyanoethyl p-toluenesulfonate
- 10 Organohaloformates
9-fluorenylmethyl chloroformate
phenyl chloroformate
4-chlorophenyl chloroformate
methyl chloroformate
15 benzyl chloroformate
vinyl chloroformate
isobutyl chloroformate
2-ethylhexyl chloroformate
ethyl chloroformate
20 2-bromoethyl chloroformate
2-chloroethyl chloroformate
1-chloroethyl chloroformate
allyl chloroformate
n-propyl chloroformate
25 butyl chloroformate
n-hexyl chloroformate
octyl chloroformate
2,2,2-trichloro-1,1-dimethylethyl chloroformate
2,2,2-trichloroethyl chloroformate
30 cholesteryl chloroformate
4-nitrophenyl chloroformate
4-nitrobenzyl chloroformate
(-)-menthyl chloroformate
4-t-butylcyclohexyl chloroformate
35 cetyl chloroformate

- (+)-1-(9-fluorenyl)ethyl chloroformate
isopropyl chloroformate
3-chlorocyclohexyl chloroformate
decyl chloroformate
5 oleyl chloroformate
octadecyl chloroformate
butenediol bischloroformate
2-chlorobenzyl chloroformate
4-chlorobutyl chloroformate
10 (+)-menthyl chloroformate
4,5-dimethoxy-2-nitrobenzyl chloroformate
cyclopentyl chloroformate
t-butylcyclohexyl chloroformate
menthylchloroformate
15 p-tolyl chloroformate
4-bromophenyl chloroformate
4-fluorophenyl chloroformate
4-methoxyphenyl chloroformate
2-nitrophenyl chloroformate
20 4-methoxycarbonylphenyl chloroformate
1-chloro-2-methylpropyl chloroformate
(+/-)-1,2,2,2-tetrachloroethyl chloroformate
2,2-dichloroethyl chloroformate
myristyl chloroformate
25 cyclohexyl chloroformate
chloromethyl chloroformate.

Organosulfonylhalides --

- 1-naphthalenesulfonyl chloride
30 dansyl chloride
2-naphthalenesulfonyl chloride
2-acetamido-4-methyl-5-thiazolesulfonyl chloride
2-thiophenesulfonyl chloride
8-quinolinesulfonyl chloride
35 benzenesulfonyl chloride

- pentafluorobenzenesulfonyl chloride
2,5-dichlorobenzenesulfonyl chloride
2-nitrobenzenesulfonyl chloride
2,4-dinitrobenzenesulfonyl chloride
5 3,5-dichloro-2-hydroxybenzenesulfonyl chloride
2,4,6-triisopropylbenzenesulfonyl chloride
2-mesitylenesulfonyl chloride
3-nitrobenzenesulfonyl chloride
p-bromobenzenesulfonyl chloride
10 4-fluorobenzenesulfonyl chloride
4-chlorobenzenesulfonyl chloride
4-chloro-3-nitrobenzenesulfonyl chloride
pipsyl chloride
4-nitrobenzenesulfonyl chloride
15 4-methoxybenzenesulfonyl chloride
4-tert-butylbenzenesulfonyl chloride
p-toluenesulfonyl chloride
trifluoromethanesulfonyl chloride
trichloromethanesulfonyl chloride
20 isopropylsulfonyl chloride
methanesulfonyl chloride
alpha-toluenesulfonyl chloride
trans-beta-styrenesulfonyl chloride
2,2,2-trifluoroethanesulfonyl chloride
25 1-hexadecanesulfonyl chloride
ethanesulfonyl chloride
2-chloroethanesulfonyl chloride
1-propanesulfonyl chloride
3-chloropropanesulfonyl chloride
30 1-butanessulfonyl chloride
methyl 2-(chlorosulfonyl)benzoate
2-nitro-4-(trifluoromethyl)benzenesulfonyl chloride
3-(trifluoromethyl)benzenesulfonyl chloride
1-octanesulfonyl chloride
35 4-(trifluoromethoxy)benzenesulphonyl chloride

(1r)-(-)-10-camphorsulfonyl chloride
d-(+)-10-camphorsulfonyl chloride
(+/-)-10-camphorsulfonyl chloride
2-nitro-alpha-toluenesulfonyl chloride.

5

Isocyanate Reagents --

trans-2-phenylcyclopropyl isocyanate
phenyl isocyanate
2-bromophenyl isocyanate
10 2-fluorophenyl isocyanate
2,4-difluorophenyl isocyanate
2,6-difluorophenyl isocyanate
2-chlorophenyl isocyanate
2,3-dichlorophenyl isocyanate
15 2,4-dichlorophenyl isocyanate
2,5-dichlorophenyl isocyanate
2,6-dichlorophenyl isocyanate
2-methoxyphenyl isocyanate
2,4-dimethoxyphenyl isocyanate
20 2,5-dimethoxyphenyl isocyanate
2-ethoxyphenyl isocyanate
2-(trifluoromethyl)phenyl isocyanate
o-tolyl isocyanate
2,6-dimethylphenyl isocyanate
25 2-ethylphenyl isocyanate
3-bromophenyl isocyanate
3-fluorophenyl isocyanate
3-chlorophenyl isocyanate
3,4-dichlorophenyl isocyanate
30 3-methoxyphenyl isocyanate
3-(trifluoromethyl)phenyl isocyanate
m-tolyl isocyanate
4-bromophenyl isocyanate
4-fluorophenyl isocyanate
35 4-chlorophenyl isocyanate

- 4-methoxyphenyl isocyanate
ethyl 4-isocyanatobenzoate
4-(trifluoromethyl)phenyl isocyanate
p-tolyl isocyanate
5 n-(chlorocarbonyl) isocyanate
benzoyl isocyanate
tert-butyl isocyanate
(s)-(-)-alpha-methylbenzyl isocyanate
isopropyl isocyanate
10 methyl isocyanate
ethyl isocyanatoacetate
octadecyl isocyanate
ethyl isocyanate
2-chloroethyl isocyanate
15 allyl isocyanate
n-propyl isocyanate
butyl isocyanate
cyclohexyl isocyanate
1-naphthyl isocyanate
20 (r)-(-)-1-(1-naphthyl)ethyl isocyanate
4-fluoro-3-nitrophenyl isocyanate
2-nitrophenyl isocyanate
3-nitrophenyl isocyanate
4-nitrophenyl isocyanate
25 2,6-diisopropylphenyl isocyanate
benzyl isocyanate
3-chloropropyl isocyanate
ethoxycarbonyl isocyanate
3,5-bis(trifluoromethyl)phenyl isocyanate
30 2,4,6-tribromophenyl isocyanate
2,5-difluorophenyl isocyanate
2,4,5-trichlorophenyl isocyanate
2,4,6-trichlorophenyl isocyanate
2-methoxycarbonylphenyl isocyanate
35 2-ethoxycarbonylphenyl isocyanate

- 2-isopropylphenyl isocyanate
- 2,3-dimethylphenyl isocyanate
- 4-methoxy-2-methylphenyl isocyanate
- 2,4-dimethylphenyl isocyanate
- 5 2,5-dimethylphenyl isocyanate
- 2-ethyl-6-methylphenyl isocyanate
- 3-cyanophenyl isocyanate
- 5-chloro-2,4-dimethoxyphenyl isocyanate
- 3-chloro-4-methylphenyl isocyanate
- 10 3,5-dichlorophenyl isocyanate
- 5-chloro-2-methoxyphenyl isocyanate
- 3,4,5-trimethoxyphenyl isocyanate
- 3,5-dimethoxyphenyl isocyanate
- 3-(methylthio)phenyl isocyanate
- 15 3-ethoxycarbonylphenyl isocyanate
- 3-acetylphenyl isocyanate
- 3,4-dimethylphenyl isocyanate
- 3,5-dimethylphenyl isocyanate
- 2-methoxy-5-methylphenyl isocyanate
- 20 3-ethylphenyl isocyanate
- 4-chloro-2-methoxyphenyl isocyanate
- 4-chloro-2-trifluoromethylphenyl isocyanate
- 4-chloro-3-trifluoromethylphenyl isocyanate
- 4-iodophenyl isocyanate
- 25 4-phenoxyphenyl isocyanate
- 4-ethoxyphenyl isocyanate
- 4-(methylthio)phenyl isocyanate
- 4-acetylphenyl isocyanate
- 4-isopropylphenyl isocyanate
- 30 4-ethylphenyl isocyanate
- 4-n-butylphenyl isocyanate
- 3-(dichloromethylsilyl)propyl isocyanate
- octyl isocyanate
- 4-methyl-3-nitrophenyl isocyanate
- 35 4-chloro-2-nitrophenyl isocyanate

- 5 2-methyl-4-nitrophenyl isocyanate
4-methyl-2-nitrophenyl isocyanate
2-fluoro-5-nitrophenyl isocyanate
2-methyl-5-nitrophenyl isocyanate
3-bromopropyl isocyanate
2,4,6-trimethylphenyl isocyanate
2-isopropyl-6-methylphenyl isocyanate
2,6-diethylphenyl isocyanate
5-chloro-2-methylphenyl isocyanate
4-chloro-2-methylphenyl isocyanate
10 4-(trifluoromethylthiophenyl)isocyanate
4-trifluoromethyl isocyanate
2,4-dibromophenyl isocyanate
2,6-dibromo-4-ethylphenyl isocyanate
2,3,4,5-tetrachloromethylphenyl isocyanate
2-chloro-5-trifluoromethylphenyl isocyanate
15 2-chloro-6-methylphenyl isocyanate
2-n-carbobutoxyphenyl isocyanate
2,4,5-trimethylphenyl isocyanate
2-methyl-6-(t-butyl)phenyl isocyanate
2-ethyl-6-isopropylphenyl isocyanate
20 2-ethyl-2-methoxyphenyl isocyanate
3-chloro-2-methylphenyl isocyanate
3-chloro-4-fluorophenyl isocyanate
4-cyanophenyl isocyanate
4-bromo-2-methylphenyl isocyanate
25 4-bromo-2,6-dimethylphenyl isocyanate
2,6-dibromo-4-fluorophenyl isocyanate
4-n-butoxyphenyl isocyanate
4-butoxycarbonylphenyl isocyanate
phenethyl isocyanate
30 2-methyl-3-nitrophenyl isocyanate
hexyl isocyanate
hexadecyl isocyanate
methylene bis(o-chlorophenyl isocyanate)
- 35

- 4-chloro-3-nitrophenyl isocyanate
2-chloro-4-nitrophenyl isocyanate
4,5-dimethyl-2-nitrophenyl isocyanate
2-chloro-5-nitrophenyl isocyanate
5 2-methoxy-4-nitrophenyl isocyanate
3-fluoro-4-methylphenyl isocyanate
5-fluoro-2-methylphenyl isocyanate
3,5-dicarbomethoxyphenyl isocyanate
2,4-dichlorobenzyl isocyanate
10 2-(methylthio)phenyl isocyanate
n-(methoxycarbonyl)isocyanate
n-(phenoxycarbonyl)isocyanate
2-biphenyllyl isocyanate
3-iodophenyl isocyanate
15 4-phenylphenyl isocyanate
tetrahydro-2-pyranyl isocyanate
4-(tert-butyl)phenylisocyanate
1-(4-bromophenyl)ethyl isocyanate
isocyanatoacetic acid n-butyl ester
20 dodecyl isocyanate
6,7-methylenedioxy-4-isocyanate-methylcoumarin
(r)-(+)-alpha-methylbenzyl isocyanate
(+/-)-1-(1-naphthyl)ethyl isocyanate
(s)-(+)-1-(1-naphthyl)ethyl isocyanate
25 3,4-difluorophenyl isocyanate
2-methoxy-5-nitrophenyl isocyanate
undecyl isocyanate
ethyl 2-isocyanato-4-methyl valerate
ethyl 6-isocyanatohexanoate
30 ethyl 2-isocyanato-4-methylthiobutyrate
ethyl 2-isocyanatopropionate
ethyl 3-isocyanatopropionate
ethyl 2-isocyanato-3-methylbutyrate
tert-butyl 3-isothiocyantopropionate
35 ethyl 2-isocyanato-3-phenylpropionate

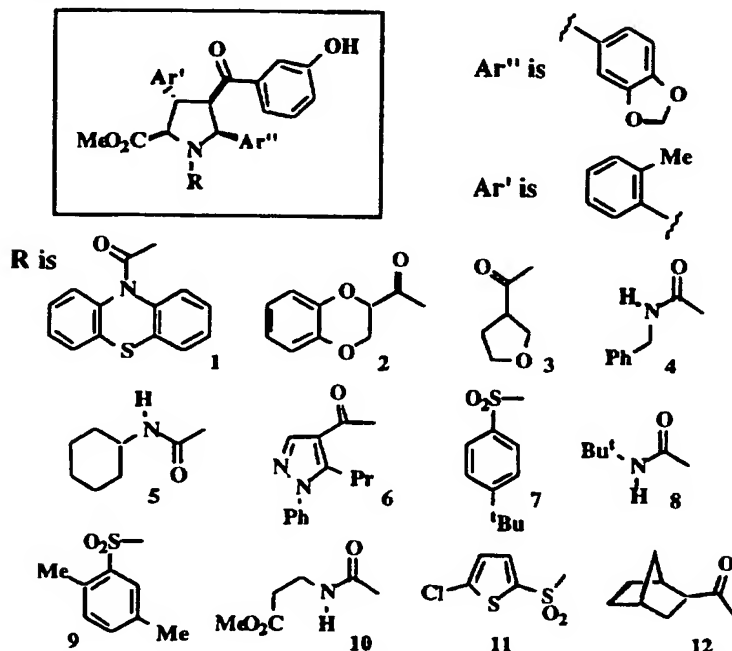
- 1,3-bis(isocyanatomethyl)cyclohexane
2-(trifluoromethoxy)phenyl isocyanate
4-(chloromethyl) phenyl isocyanate
1-adamantyl isocyanate
5 1,3-bis(2-isocyanato-2-propyl)benzene
n-amyl isocyanate
n-heptyl isocyanate
2-chloroethyl isocyanate, [ethyl-1,2-14c]
1,1,3,3-tetramethylbutyl isocyanate
10 3,5-dinitrophenyl isocyanate

Organic Isothiocyanates --

- cyclohexyl isothiocyanate
1-naphthyl isothiocyanate
15 trimethylsilyl isothiocyanate
phenyl isothiocyanate
2-bromophenyl isothiocyanate
2-fluorophenyl isothiocyanate
2-chlorophenyl isothiocyanate
20 o-tolyl isothiocyanate
3-bromophenyl isothiocyanate
3-fluorophenyl isothiocyanate
3-chlorophenyl isothiocyanate
m-tolyl isothiocyanate
25 4-bromophenyl isothiocyanate
4-fluorophenyl isothiocyanate
4-chlorophenyl isothiocyanate
p-tolyl isothiocyanate
ethoxycarbonyl isothiocyanate
30 benzoyl isothiocyanate
tert-butyl isothiocyanate
tert-octyl isothiocyanate
methyl isothiocyanate
benyl isothiocyanate
35 ethyl isothiocyanate

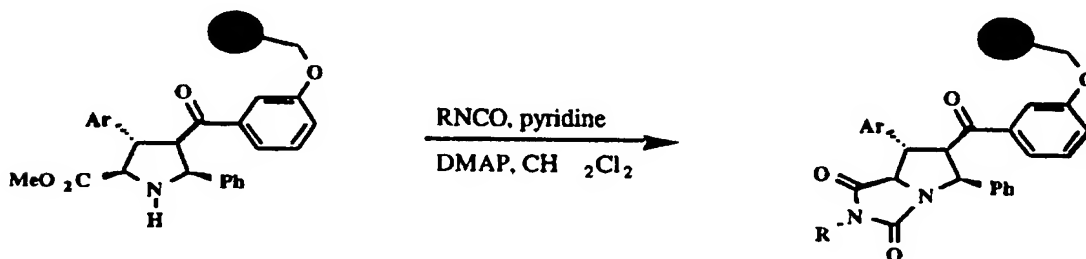
phenethyl isothiocyanate
allyl isothiocyanate

Preferred groups for acylation of the pyrrolidine nitrogen
are as follows:



Part b - Formation of hydantoins

The groups R₁ and R₂ may form a hydantoin ring. When
hydantoin structures are desired the alkylating/acylating
agent is an isocyanate or isothiocyanate. A hydantoin
forming reaction is illustrated by the following scheme:

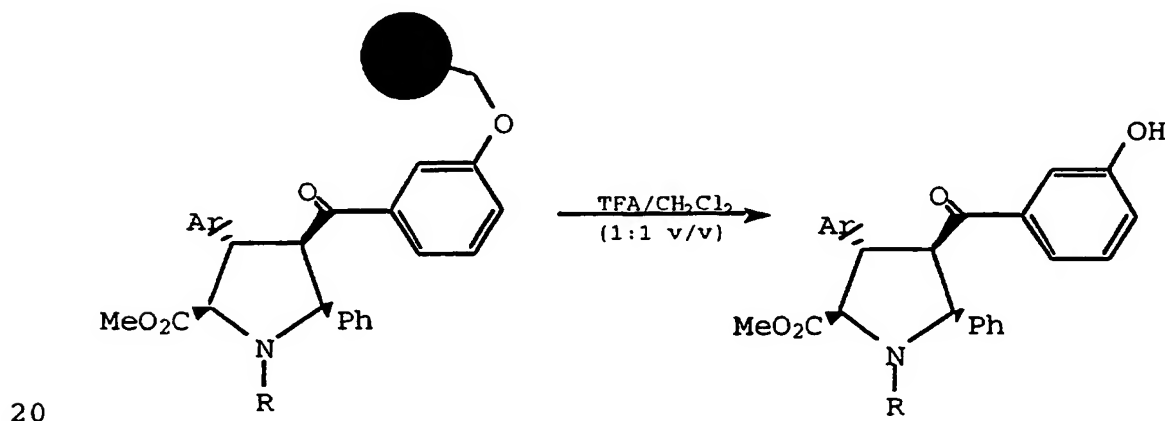


Suitable isocyanate reactants for hydantoin formation
were described in the preceding listings the disclosure of
which is incorporated herein by reference.

The solid support-pyrrolidine compounds produced at this step in the process of the invention are themselves valuable stable, and storable intermediates which may used
5 when needed as sources of individual library compounds. Individual library compounds are made from these intermediates by cleavage as described in the following process Step (E).

10 Step E. - Library compound cleavage from Solid Support.

The final step of the process for preparing combinatorial pyrrolidine libraries is separation of the library compounds from its solid support. For polymeric
15 solid supports of the Wang Resin type the decoupling is conventionally done with strong acids. For Example, the following reaction employing TFA with a Wang resin supported pyrrolidine may be used.

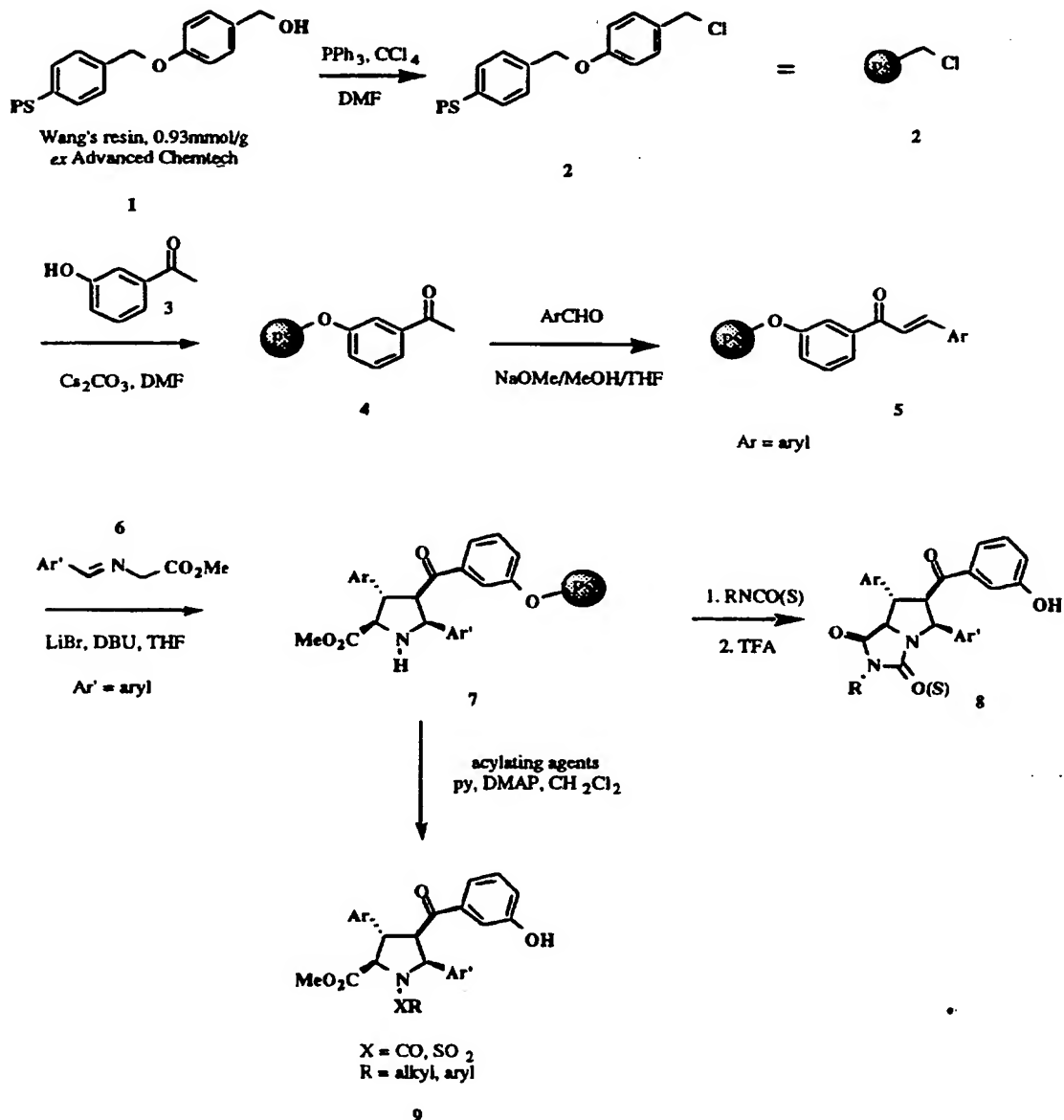


The final step in the pyrrolidine library forming process of the invention may be supplemented by purification techniques such as chromatography, crystallization, distillation, solvent extraction, or combinations of such
25 techniques.

REACTION SCHEME 1

An illustrative reaction scheme illustrating all steps of the pyrrolidine combinatorial library process in combination is shown below:

5



The following example illustrates the preparation of a pyrrolidine combinatorial library with reference to Scheme 1, supra.

5

Chlorination of Wang Resin 1

Wang resin 1 (5g, 100-200 mesh, 0.93mequiv/g, ex Advanced Chemtech) was suspended in anhydrous DMF (60ml). To this was
10 added triphenyl phosphine (4.88g, 18.6mmol) and then carbon tetrachloride (1.80ml, 18.6mmol). The reaction vessel was capped and placed on an orbital shaker for 2 days. At this time the reaction mixture was filtered and washed with the following: THF (200ml), THF-H₂O (1:1, 200ml), THF (200ml)
15 and finally MeOH (200ml). The resulting white resin was dried in vacuo to provide 5.04g of chlorinated Wang resin 2. Anal. found: C, 87.46, H, 7.45, Cl, 2.83.

Coupling of 3-Hydroxyacetophenone 3 to Chlorinated Wang
20 Resin 2

Chlorinated Wang resin 2 (3.82g) , 3-hydroxyacetophenone (ex Aldrich) 3 (1.56g, 11.46mmol), cesium carbonate (3.73g, 11.46mmol) and sodium iodide (0.69g, 4.58mmol) were combined
25 together in anhydrous DMF (50ml), capped and placed on an orbital shaker for 3 day. The reaction mixture was filtered and washed successively with the following solvents (50ml each): DMF, MeOH, H₂O, DMF-MeOH, DMF, CH₂Cl₂, MeOH. Following the final wash, the resin was dried overnight in
30 vacuo to provide an off-white resin 4 (4.20g): IR(KBr) 1675cm⁻¹. Anal. found C, 88.34, H, 7.32. The loading of this resin was determined by cleavage of a known amount and HPLC analysis. Thus the resin (51.2mg) was suspended in TFA (1ml) and stirred for 20hr. HPLC analysis

indicated 3.42 mg of 3-hydroxyacetophenone 3 had been cleaved. This corresponds to a loading of 0.49mmol/g.

Preparation of Enone 5 (Ar=p-CH₃OMe) by Condensation

5 Reaction of 3-Hydroxyacetophenone Resin 4

A solution of NaOMe in MeOH (31.3ml of a 0.5M solution in MeOH, 15.6mmol) was added to a mixture of acetophenone resin 4 (2.66g) and p-anisaldehyde (2.36g, 15.6mmol) in anhydrous THF (30ml). The flask was capped and placed on an orbital shaker for 4 day. The reaction mixture was filtered and washed successively with the following solvents (50ml of each): THF, MeOH, THF, MeOH and finally THF. The resin was dried with air pulling through the Buchner funnel to give 15 3.0g of a light yellow resin 5 (Ar=p-C₆H₄OMe).

A small sample was suspended in TFA and stirred for 20 hr. The supernatant liquid was decanted and evaporated. The resulting oil was re-evaporated from methylene chloride several times to give an off white solid. ¹H NMR (CDCl₃) of 20 this material was identical to a sample of enone prepared independently by standard solution synthesis.

Preparation of Pyrrolidine 7 (Ar=p-C₆H₄OMe) via 1,3-Dipolar Cycloaddition of Imine 6 (Ar'=Ph)

25

Resin 5 (Ar=OMe) (1g) was suspended in anhydrous THF. To this was added sequentially imine 6 (Ar'=Ph) (434mg as a solution in dry THF), LiBr (255mg, 2.94mmol) and DBU (372mg, 2.45mmol). The reaction mixture was slowly stirred for 3 day 30 at which time the resin was filtered and washed successively with MeOH, THF, MeOH, THF, MeOH, THF, CH₂Cl₂ and air dried to give resin 7.

Acetylation of Pyrrolidine Resin 7 (Ar=p-C₆H₄OMe, Ar'=Ph)

Resin 7 (Ar=p-C₆H₄OMe, Ar'=Ph) (300mg) was suspended in anhydrous methylene chloride. To this was added DMAP (3mg),
5 pyridine (190μl, 2.35mmol) and acetyl chloride (1.18ml of a 1M solution in methylene chloride, 1.175mmol). The mixture was stirred at ambient temperature for 20hr, at which time the resin was filtered and washed sequentially with the following solvents (10ml each): CH₂Cl₂, DMF, MeOH, DMF,
10 MeOH, DMF, CH₂Cl₂, and further CH₂Cl₂. The resin was air dried and suspended in a 1:1 (v/v) mixture of CH₂Cl₂:TFA and stirred at ambient temperature for 20hr. The supernatant liquid was removed by filtration and the resin washed several times with methylene chloride. The filtrates were
15 evaporated in vacuo to yield a crude brown foam (90mg). Purified by chromatography (SiO₂, 3:2 EtOAc-hexanes) to afford pyrrolidine 9 (31mg) (Ar=p-C₆H₄OMe, Ar'=Ph, X=CO, R=Me). Crystallised from methanol. Anal. calcd. for C, .H, N, . Found C, .H, .N, .

20

Synthesis of Bicyclic Hydantoin 8 (Ar=p-C₆H₄OMe, Ar'=Ph, R=n-Bu)

Pyrrolidine resin 7 (Ar=p-C₆H₄OMe, Ar'=Ph) was suspended in
25 methylene chloride containing DMAP (1mg) and pyridine (103μl, 1.28mmol). Butyl isocyanate (0.40ml of a 1M solution in methylene chloride, 0.40mmol) was added and the mixture stirred at ambient temperature for 20hr. The resin was filtered and washed sequentially with the following solvents
30 (15ml each of): CH₂Cl₂, DMF, MeOH, DMF, MeOH, DMF, CH₂Cl₂. The resin was air dried and suspended in a 1:1 (v/v) mixture of CH₂Cl₂:TFA and stirred at ambient temperature for 20hr. The supernatant liquid was removed by filtration and the resin washed several times with methylene chloride. The
35 filtrates were evaporated in vacuo to yield a crude brown

foam (19mg). Purified by preparative TLC (SiO₂, 3% MeOH-CH₂Cl₂) to afford bicyclic hydantoin **8** (Ar=p-C₆H₄OMe, Ar'=Ph, R=Bu) as a white solid. Crystallised from MeOH. FAB MS 499 (M+1). Anal. calcd. for C₃₀H₃₀N₂O₅ C, 72.27. H, 6.06. N, 5.61. Found: C, 72.38. H, 6.12. N, 5.65.

Experimental Conditions for Combinatorial Plate Synthesis

Resin Preparation

10

Sodium methoxide (29.13g, 0.539mol) was added to a stirred mixture of Merrifield resin **1** (80g of 2-2.5mmol/g, ex Acros) and 4-hydroxybenzylalcohol (66.95g, 0.539mol, ex Aldrich) in DMA. The reaction mixture was heated to 55°C for 8hr and allowed to cool. Filtered and washed (400ml, 2 times) successively with dioxane, DI water, dioxane, dioxane-DI water (1:1 v/v), dioxane, MeOH and dried to give an off-white resin (81g).

20 This resulting resin (81g) and dichlorotriphenylphosphorane (235g, 0.728mol) were combined in dry methylene chloride (1 litre) and stirred for 2 days, at which time it was filtered and washed successively (500ml of each) with methylene chloride, methanol, methylene chloride, methanol, methylene chloride. The resin was dried in vacuo (35°C) to afford a white resin **2** (80.1g).

30 Chlorinated Wang resin **2** (70.0g), 3-hydroxyacetophenone **3** (64.2g, 0.472mol, ex Aldrich), cesium carbonate (102.5g, 0.315mol, ex Fluka) and sodium iodide (23.6g, 0.157mol, ex Fluka) were combined in dry DMF (800ml) and stirred at ambient temperature for 3 days. The mixture was filtered and washed successively with DMF, MeOH, DI water, THF, DI water, THF, MeOH, and dried in vacuo overnight to afford a light brown resin **4** (81.2g).

35

Plate Synthesis

3-Hydroxy acetophenone resin 4 (35.3g) was suspended in a ca. 1:1 (v/v) mixture of DMF:CH₂Cl₂ (650ml) to obtain an isopicnic slurry. This was distributed to 13 x 96-well plates (0.50ml to each well, corresponds to ca. 27mg/well [ca. 29umol/well]). The wells were allowed to drain and were washed with THF via an 8-way manifold several times, drained and pulled dry over a vacuum plenum.

10

1) Condensation Reaction: To each row in a 96-well plate was added a unique aryl aldehyde (400µl of a 1M solution in THF, 14 equiv) and was followed by addition (to every well) a solution of sodium methoxide (500µl of a 0.5M solution in methanol, 8.6 equiv., ex Aldrich). The wells were capped and tumbled for 3-4 day.

The wells were uncapped, filtered and washed successively with the following solvents (500µl of each): THF, MeOH, THF, MeOH, THF, MeOH, THF, and pulled dry under a vacuum plenum.

2) 1,3-Dipolar Cycloaddition Reaction: To each well was added in sequence the following reagents via 8-way manifold: a) benzaldehyde imine of glycine (188µl of a 1M solution in THF, 6.5equiv.), b) LiBr (500µl of a 0.5M solution in THF, 8.6equiv.) and c) DBU (188µl of a 1M solution in THF, 6.5equiv.). The wells were capped and tumbled for 3-4 days, at which time the resin was washed successively with the following solvents (500µl of each): THF, MeOH, THF, MeOH, THF, MeOH, THF, CH₂Cl₂ and pulled dry under a vacuum plenum.

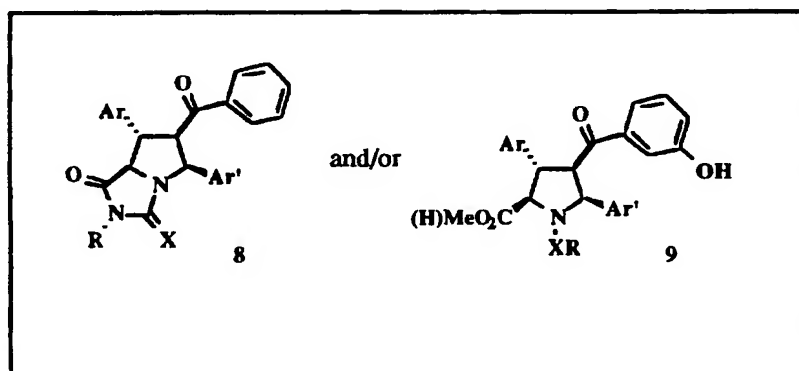
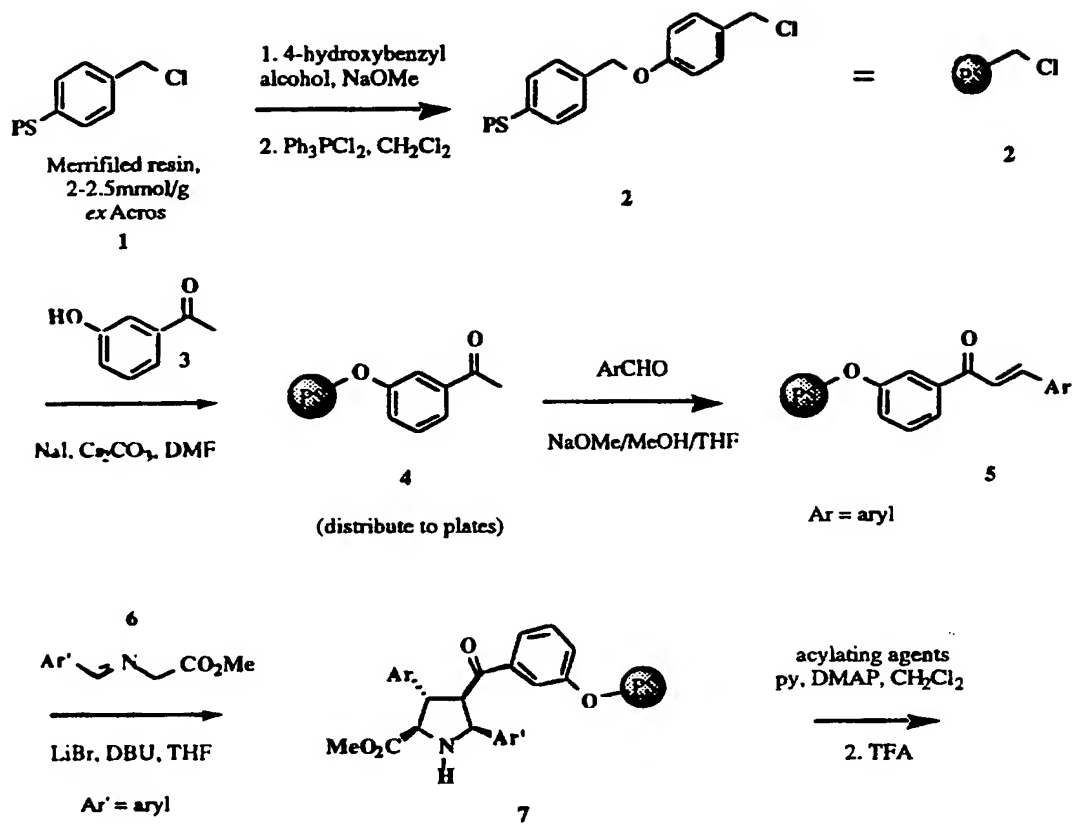
3) Acylation Reaction: To each well was added via 8-way manifold a solution of pyridine and DMAP in CH₂Cl₂ (35.1µl pyridine and 0.53mg DMAP in 400µl CH₂Cl₂ total volume) and this was followed by a solution of unique acylating agent to each row (1-8) (400µl of 1M solution in CH₂Cl₂). The plates were capped and tumbled for 20hr, filtered and washed successively with the following solvents (500µl of each):

CH₂Cl₂, DMF, MeOH, DMF, MeOH, and CH₂Cl₂. The resin was dried under a vacuum plenum.

- 4) Cleavage from the Resin: To each well was added via 8-way manifold a solution of TFA in CH₂Cl₂ (750μl of a 10% solution). The plates were capped and tumbled for 20hr. The wells were then uncapped and allowed to gravity filter to a 1ml 96 well plate. The resin was washed with 125μl CH₂Cl₂ (each well) and the solvents evaporated in a speed-vac. TLC's were obtained after re-dissolving in 10%MeOH-CH₂Cl₂.

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Experimental for Plate Synthesis



R is alkyl and/or aryl
 X = O or S

This invention is particularly well suited as a general method for preparing a structurally diverse pyrrolidine library. The final form of the library compounds in the pyrrolidine library may be as a solute dissolved in a solvent (viz., the reaction medium) or the solvent may be removed and the final product retained as a powder, paste or oil.

The reaction zone for forming each pyrrolidine library compound of this invention contains a solvent. The solvent reaction medium is typically a solvent for the reactants used.

The utility of the method of the invention and the pyrrolidine library created thereby is for developing new drugs. Pharmaceutical drug discovery relies heavily on studies of structure-activity relationships wherein the structures of discovered "lead compounds" are the basis for new drug development. The method of the invention systematically and simultaneously generates large numbers of diverse pyrrolidine molecules useful as a source of lead compounds. The combinatorial pyrrolidine libraries of the invention may be screened for pharmacologically active compounds using conventional screen protocols known in the art for any targeted disease state. Certain library compounds prepared by the process of the invention.

The successful practice of combinatorial chemistry is best done by confining reactants, products, and assay materials in specially defined arrays, adaptable to automated methods. Automated methods, optionally, software driven and computer assisted, permits full exploitation of combinatorial chemistry for diverse library preparation. For example, pipetting, diluting, dispensing, data collection, storage, plate heating/cooling, plate washing, measurements (fluorescent/radiographic/colorimetric), data

collection and high-capacity operation are all adaptable to automation.

5 Wellplate Apparatus containing library compounds prepared by the process of the invention:

The processes of making the pyrrolidine library of the invention may be conveniently carried out in a wellplate apparatus such as illustrated in Fig. 1 and Fig. 2, hereinafter described. It is particularly advantageous to carry out the method of the invention in a standard wellplate apparatus such as a plastic 96 well microtiter plate.

Typically, the wellplate apparatus is in the form of a rigid or semi-rigid plate, said plate having a common surface containing openings of a plurality of vessels arranged in rows and columns. A standard form of wellplate apparatus is a rectangular plastic plate having 8 rows and 12 columns (total 96) of liquid retaining depressions on its surface. A wellplate apparatus may optionally have other elements of structure such as a top or cover (e.g., plastic or foil), a bottom in a form such as a plate or reservoir, clamping means to secure the wellplate and prevent loss of its contained compounds.

25 The sequence of operations to be used for library generation with the wellplate is as follows:

The wellplate apparatus of the invention:

A wellplate inoculated with the novel pyrrolidine library compounds of the invention is itself a new construct or apparatus which has particular utility in an assay kit used to discover lead compounds. A suitable system of operation and related apparatus are made as follows:

1. Reaction zones are made by drilling 96 holes in the bottom of 96 deepwell titer plates and putting a porous frit in the bottom of each well.

2. The plate is put in a clamp assembly to seal the
5 bottom of the wells.

3. Synthesis is begun by adding reagents to their assigned plate coordinates (reaction zone).

4. The plate is capped then tumbled to mix the reagents.

10 5. Solid supported scavenger is added to each reaction zone after completion of the reaction is shown by thin layer chromatography.

6. After sufficient reaction time the plate is removed from the clamp and the resin washed.

15 7. The solution containing product is filtered and the solution collected by transfer into another 96 well plate.

8. The reaction products (library compounds) are analyzed by thin layer chromatography.

20 FIG. 1 illustrates the top surface of a wellplate apparatus of the invention. The wellplate (3) is a plastic plate with 96 wells (depressions) capable of holding liquids. When used in the parallel array synthesis individual reaction products are prepared in each well and
25 are labeled by the wellplate coordinates. The shaded circles in the Figure represent wells filled with pyrrolidine library compounds prepared by the solution phase combinatorial processes of the invention. The library compound at location (1), for example, is identified by the
30 alphanumeric coordinate, "A6."

FIG. 2 illustrates a side view of a wellplate apparatus used in the Assay Kit of the invention. The wellplate (5) contains wells (7) with a filter (9) and liquid reaction medium containing scavenger (11). The wells have an outlet
35 at bottom which is sealed by gasket (13) held in place by

top cover (15) and bottom cover (17) maintained in position by clamp (19).

5 Assay Kits using wellplates with the library compounds of the invention:

This invention includes an assay kit for identification of pharmaceutical lead compounds. The assay kit comprises as essential parts, (i) wellplate apparatus (containing in its wells the pyrrolidine library compounds of the
10 invention), and (ii) biological assay materials.

The wellplate apparatus in the kit may comprise a set of wellplate apparatus such as illustrated in Fig. 1. The library compounds contained in each wellplate may be prepared by either the pyrrolidine combinatorial library
15 forming process taught herein. Preferably the wellplate apparatus has the form of a standard 96 well microtiter plate.

The assay kit also contains biological assay materials. These biological assay materials are generally in vitro
20 tests known to be predictive of success for an associated disease state. Illustrative of biological assay materials useful in the kit of this invention are those required to conduct the following assays:

In vitro assays:

25 Enzymatic Inhibition
 Receptor-ligand binding
 Protein-protein Interaction
 Protein-DNA Interaction

Cell-based, Functional assays:

30 Transcriptional Regulation
 Signal Transduction/ Second Messenger
 Viral Infectivity

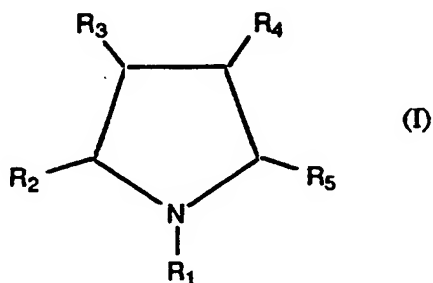
Add, Incubate, & Read assays:

 Scintillation Proximity Assays
35 Angiotensin II SPA receptor binding assay

- Endothelin converting enzyme [^{125}I] SPA
assay
HIV proteinase [^{125}I] SPA enzyme assay
Cholesteryl ester transfer protein (CETP)
5 [^3H] SPA assay
Fluorescence Polarization Assays
Fluorescence Correlation Spectroscopy
Colorimetric Biosensors
Ca $^{2+}$ -EGTA Dyes for Cell-based assays
10 Reporter Gene Constructs for cell based assays
 Luciferase, green fluorescent protein,
 b-lactamase
 Electrical cell impedance sensor assays
 Strep Potentiator Assay
15 The Strep Potentiator Assay is for antibiotic therapeutic
 indication.
 The assay has a two plate format:
 Into plate 1 compounds to be tested are added with medium,
 methicillin, and a methicillin resistant *Staphylococcus*
20 aureus. After an overnight incubation, the plates are read
 on a plate reader at 650 nm.
- The utility of the pyrrolidine library compounds of
this invention is illustrated by their expected positive
25 impact in at least one of the assays cited above.
- While the present invention has been illustrated above
by certain specific embodiments, it is not intended that
these specific examples should limit the scope of the
30 invention as described in the appended claims.

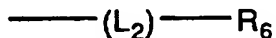
What is claimed is:

1. A library of substituted pyrrolidine compounds wherein said library contains a plurality of diverse library
5 compounds, wherein each library compound has the formula (I):

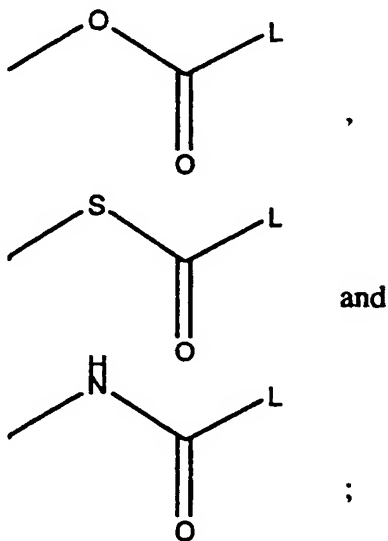


wherein;

- 10 R_1 is an electrophilic group;
 R_2 is a group represented by the formula:



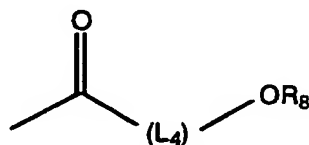
- where divalent linking group $-(L_2)-$ is selected from the
 15 group consisting of,



L is the point of attachment of the divalent group to the pyrrolidine ring, R₆ is a non-interfering substituent, and R₁ and R₂ may join together to form a hydantoin ring;

R₃ is an aromatic group;

5 R₄ is a group of the general formula,



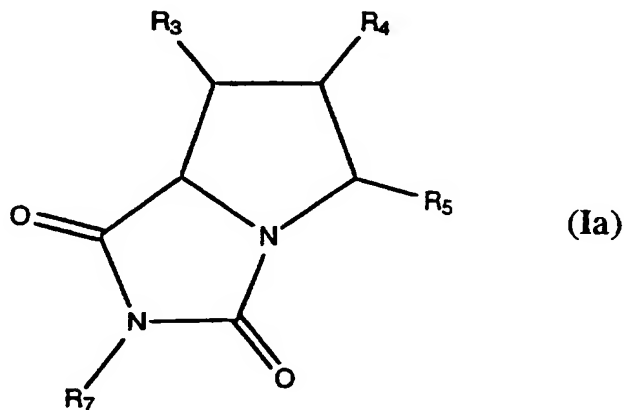
where -(L₄)- is a divalent linking group, R₈ is hydrogen or a

10 non-interfering substituent; and

R₅ is an aromatic group.

2. The library of claim 1 represented by the formula (Ia),

15



wherein R₇ is a non-interfering substituent.

20

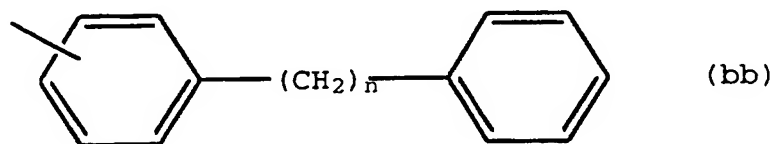
3. The pyrrolidine library of claim 1 wherein;

R₁ is an electrophilic group derived from an electrophilic reagent having a molecular weight of from about 30 to about 600 selected from the group consisting of; organic halides, acyl halides, sulfonic acid esters,

organohaloformates, organosulfonyl halides, organic isocyanates, and organic isothiocyanates;

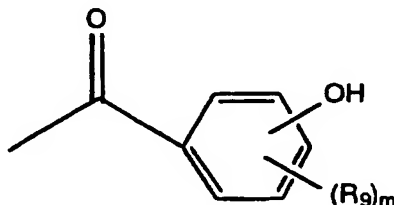
R₂ is -CO₂(C₁-C₁₀ alkyl);

R₃ and R₅ are independently aromatic groups selected
 5 from the group consisting of substituted or unsubstituted heterocyclic groups derived from pyrrolyl, furanyl, thiophenyl, pyrazolyl, imidazolyl, phenylimidazolyl, triazolyl, isoxazolyl, oxazolyl, thiazolyl, thiadiazolyl, indolyl, carbazolyl, norharmanyl, azaindolyl, benzofuranyl,
 10 dibenzofuranyl, dibenzothiophenyl, indazolyl, imidazo(1,2-pyridinyl, benzotriazolyl, anthranilyl, 1,2-benzisoxazolyl, benzoxazolyl, benzothiazolyl, purinyl, pyridinyl, dipyridyl, phenylpyridinyl, benzylpyridinyl, pyrimidinyl, phenylpyrimidinyl, pyrazinyl, 1,3,5-triazinyl, quinolinyl,
 15 phthalazinyl, quinazolinyl, and quinoxalinyl and carbocyclic groups derived from phenyl, naphthyl, tolulyl, xylenyl, indenyl, stilbenyl, terphenyl, diphenylethylenyl, phenylcyclohexenyl, acenaphthylenyl, and anthracenyl, biphenyl, bibenzyl and related bibenzyl homologues represented by
 20 the formula (bb),



where n is a number from 1 to 8; and

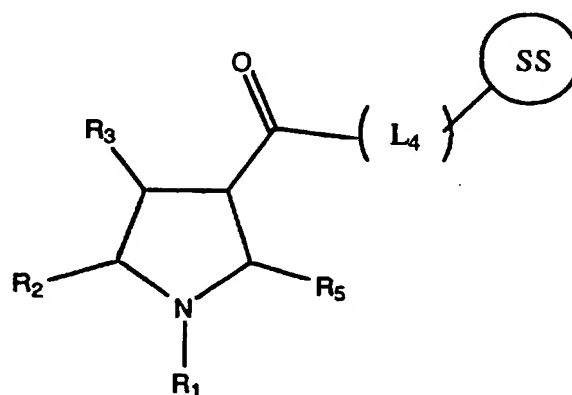
25 R₄ is



where R₉ is a non-interfering group and m is an integer from 0 to 3.

4. The individual substituted pyrrolidine library compounds of the library of claim 1.

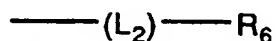
5. A library of intermediate substituted pyrrolidine compounds comprising a plurality of diverse compounds, wherein each intermediate has the formula (X):



10 wherein;

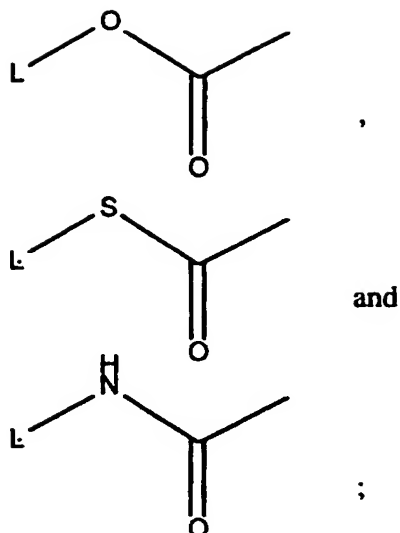
R₁ is an electrophilic group;

R₂ is a group represented by the formula:



15 where divalent linking group $\text{---}(L_2)\text{---}$ is selected from the group consisting of,

71



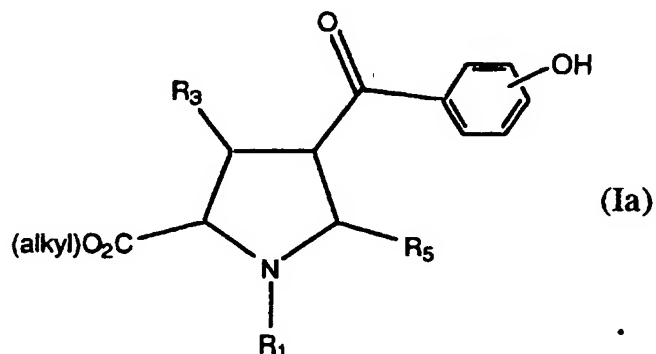
- L is the point of attachment of the divalent group to the pyrrolidine ring, R₆ is a non-interfering substituent, and
- 5 R₁ and R₂ may join together to form a hydantoin ring;
 R₃ is an aromatic group;
 -(L₄)- is a divalent linking group,

(SS)

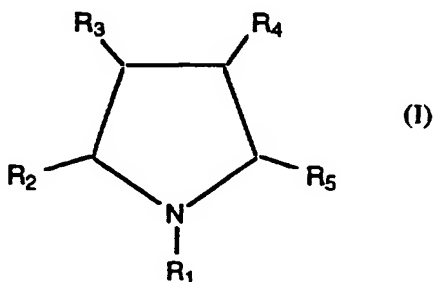
- is a solid support; and
- 10 R₅ is an aromatic group.

6. The intermediate substituted pyrrolidine compounds of claim 5.

7. The library of Claim 1 comprising a plurality of diverse library compounds, wherein each library compound is represented by Formula (Ia):



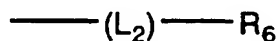
8. A combinatorial process for preparing a library of substituted pyrrolidine compounds, said library comprising a plurality of diverse library compounds, wherein each library compound is made in a separate reaction zone and is represented by the formula (I):



15 wherein;

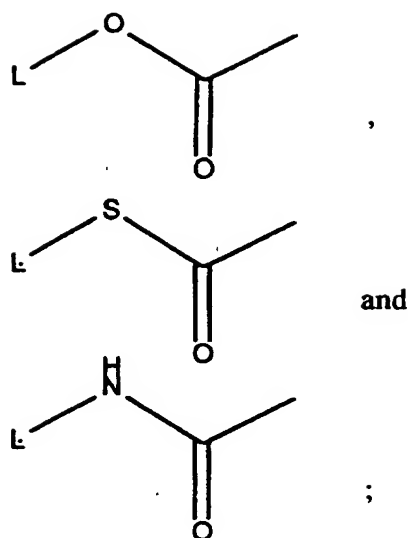
R₁ is an electrophilic group;

R₂ is a group represented by the formula:



20 where divalent linking group -(L₂)- is selected from the group consisting of,

73

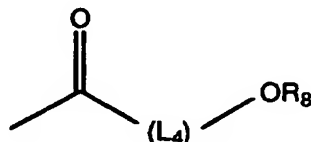


L is the point of attachment of the divalent group to the pyrrolidine ring, R₆ is a non-interfering substituent, and

5 R₁ and R₂ may join together to form a hydantoin ring;

R₃ is an aromatic group;

R₄ is a group of the general formula,



10 where $-(\text{L}_4)-$ is a divalent linking group, R₈ is hydrogen or a non-interfering substituent; and

R₅ is an aromatic group;

wherein said process comprises the steps of;

15 A) Methyl ketone functionalizing a Wang resin solid support;

B) forming an aromatic enone on the Wang resin reaction product of Step (A);

C) reacting an azomethine ylide with the reaction product of Step (B) to effect 1,3-dipolar cycloaddition;

20 D) reacting an electrophile with the reaction product of Step (C) to effect electrophilic substitution on the pyrrolidine nitrogen; and

E) cleaving the substituted-diamino pyrrolidine reaction product of Step (D) from the solid support with strong acid, then recovering each pyrrolidine library compound.

5

9. The process of step 8 wherein;

in step (A) methyl phenyl ketone is used to functionalize the Wang resin;

10 in step (B) the aromatic aldehyde used to form the enone is a phenyl or substituted phenyl aldehyde;

in step (C) the azomethine ylide is a C₁-C₁₀ alkyl ester of glycine; and

15 in step (D) the electrophilic agent has a molecular weight of from about 15 to about 600 and is selected from the group consisting of; organic halides, acyl halides, sulfonic acid esters, organohaloformates, organosulfonyl halides, organic isocyanates, and organic isothiocyanates.

20 10. An assay kit for identification of pharmaceutical lead compounds, comprising biological assay materials and wellplate apparatus;

wherein the improvement comprises using as wellplate apparatus a wellplate containing in each well the individual library compounds of a diverse combinatorial pyrrolidine
25 library prepared by the process of claim 8.

11. The assay kit of claim 10 containing biological assay materials selected from the group of assay tests;

In vitro assays:

30 Enzymatic Inhibition
 Receptor-ligand binding
 Protein-protein Interaction
 Protein-DNA Interaction
 Cell-based, Functional assays:
35 Transcriptional Regulation

Signal Transduction/ Second Messenger

Viral Infectivity

Add, Incubate, & Read assays:

Scintillation Proximity Assays

- 5 Angiotensin II SPA receptor binding assay
 Endothelin converting enzyme [^{125}I] SPA
 assay
 HIV proteinase [^{125}I] SPA enzyme assay
 Cholesteryl ester transfer protein (CETP)
10 [^3H] SPA assay

Fluorescence Polarization Assays

Fluorescence Correlation Spectroscopy

Colorimetric Biosensors

Ca^{2+} -EGTA Dyes for Cell-based assays

- 15 Strep Potentiator Assay.
 Reporter Gene Constructs for cell based assays
 Luciferase, green fluorescent protein,
 b-lactamase, and
 Electrical cell impedance sensor assays.

20

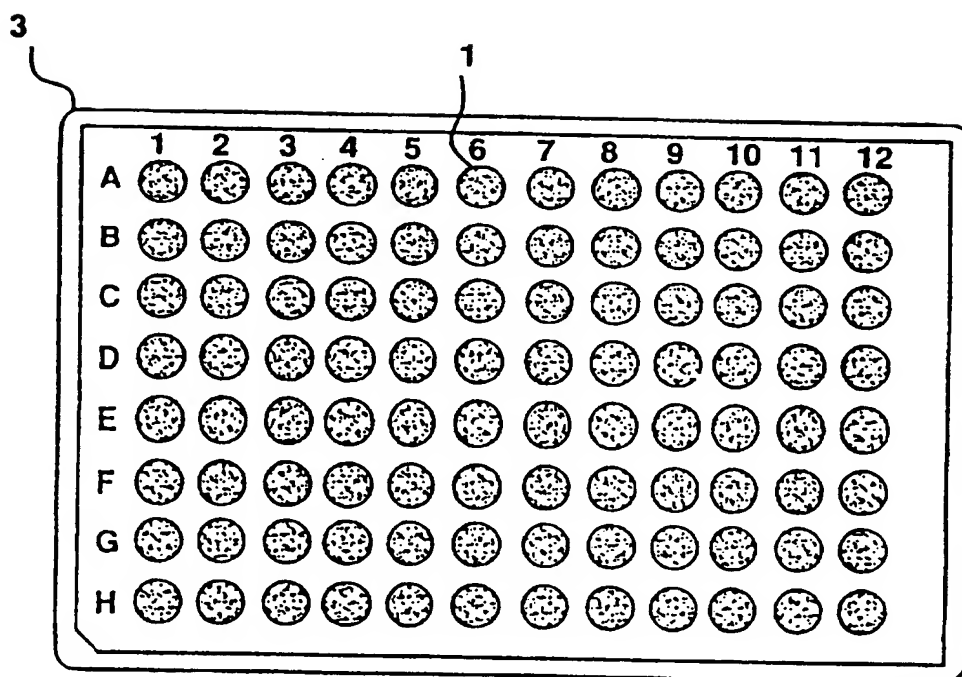
12. Wellplate apparatus suitable as a replaceable
element in an automated assay machine wherein the
improvement comprises;

- 25 using as the wellplate apparatus a diverse pyrrolidine
combinatorial wellplate, wherein each well contains a
pyrrolidine library compound prepared by the method of
claim 8.

13. The apparatus of claim 12 comprising a 96 well
30 microtiter plate.

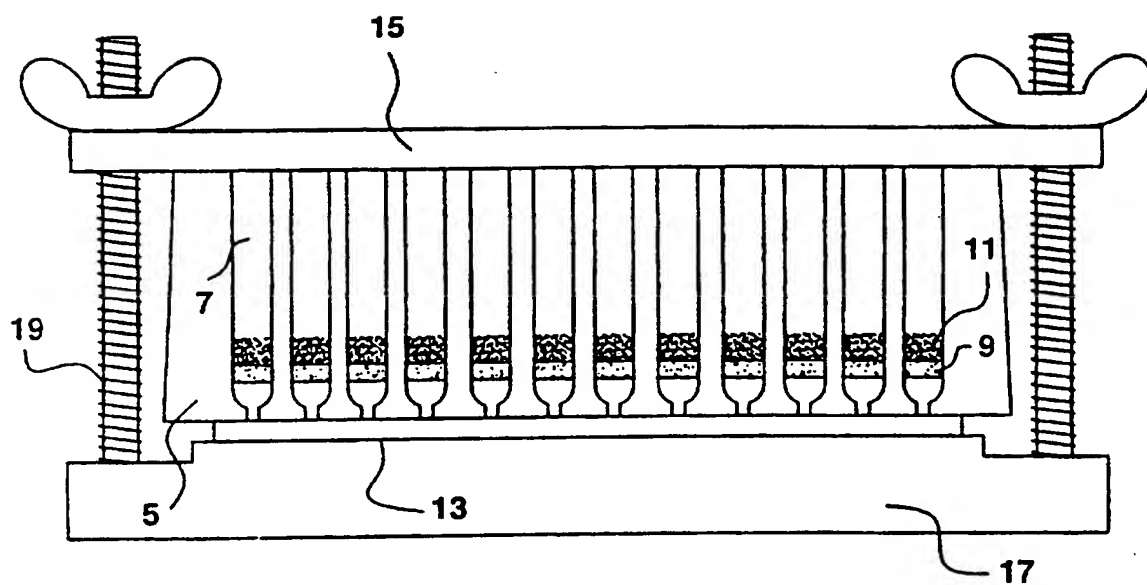
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FIG. 1



2 / 2

FIG.2



SUBSTITUTE SHEET (RULE 26)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US97/14559

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 544/237, 242, 264, 336, 353; 546/348; 548/127, 146, 215, 255, 262.2, 335.1, 440, 490, 571

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, CAS ONLINE, MEDLINE

search terms: combinatorial, librar?, pyrrolidin?, hydantoin

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,525,734 A (GALLOP et al.) 11 June 1996, see entire document.	1, 3, 7-9, 12-13
Y	US 5,525,735 A (GALLOP et al.) 11 June 1996, see entire document.	1, 3, 7-9, 12-13
Y	MURPHY et al. Combinatorial Organic Synthesis of Highly Functionalized Pyrrolidines: Identification of a Potent Angiotensin Converting Enzyme Inhibitor from a Mercaptoacyl Proline Library. J. Am. Chem. Soc. 05 July 1995, Vol. 117, No.26, pages 7029-7030, see entire document.	1, 3, 7-9, 12-13
Y	ARMSTRONG et al. Multiple-Component Condensation Strategies for Combinatorial Library Synthesis. Acc. Chem. Res. March 1996, Vol.29, No.3, pages 123-131, see entire document.	1, 3, 7-9, 12-13

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
B earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search	Date of mailing of the international search report
02 OCTOBER 1997	10 NOV 1997

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
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Authorized officer

JANE C. OSWECKI

Telephone No. (703)308-1235

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/14559

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1, 3, 7

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet(1))(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/14559

A. CLASSIFICATION OF SUBJECT MATTER: IPC (6):

C07D 207/08, 209/08, 209/86, 211/82, 213/34, 213/38, 213/40, 213/50, 213/56, 215/46, 233/61, 237/30, 239/20, 241/12, 241/36, 249/08, 263/32, 277/28, 285/12, 403/04, 413/04, 413/14, 417/04, 417/14, 473/00

A. CLASSIFICATION OF SUBJECT MATTER: US CL :

544/237, 242, 264, 336, 353; 546/348; 548/127, 146, 215, 255, 262.2, 335.1, 440, 490, 571

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1.

Group I, claims 1, 3 and 7, drawn to a combinatorial library of pyrrolidine derivative compounds.

Group II, claim 2, drawn to a combinatorial library of hydantoin derivative compounds.

Group III, claim 4, drawn to pyrrolidine derivative compounds having quinoxaline, triazine or pyrazine as substituents.

Group IV, claim 4, drawn to pyrrolidine derivative compounds having phthalazine, pyrimidine, purine or quinazoline as substituents.

Group V, claim 4, drawn to pyrrolidine derivative compounds having thiazole, thiadiazole, oxazole, isoxazole, benzoxazole or triazole as substituents.

Group VI, claim 4, drawn to pyrrolidine derivative compounds having imidazole, indazole, carbazole or indole as substituents.

Group VII, claim 4, having imidazo-pyridine, azaindole or pyridine as substituents.

Group VIII, claims 5-6, drawn to a library of pyrrolidine derivative intermediate compounds.

Group IX, claims 10 and 11, drawn to an assay kit for pharmaceutical lead compounds.

Claims 8, 9, 12 and 13 are generic to any group paid for.

The inventions listed as Groups I-IX do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Groups I-VIII are drawn to compounds, and Group IX is drawn to an assay kit. Groups I, II and VIII are drawn to libraries of compounds with each library being drawn to compounds that differ in structure from compounds in the other two libraries and with each library of compounds not being known equivalents in the art. Groups III-VII, drawn to pyrrolidine derivative compounds, differ each from the other because no two groups share a special technical feature which makes a contribution over the prior art with any other group. Each of these groups is drawn to compounds that are structurally different and are not known as equivalents in the art.